



醫院管理局  
HOSPITAL  
AUTHORITY

Infectious Disease Control  
Training Centre  
傳染病控制培訓中心



衛生防護中心  
Centre for Health Protection  
Infection Control Branch  
感染控制處

## INFECTIOUS DISEASE FORUM: HUMAN PAPILLOMA VIRUS – NEXT STEPS

# Towards the elimination of HPV

**Richard Hillman**

**June 11th 2018**



**DACS**  
Dysplasia and Anal Cancer Services

# Potential Conflicts of Interest Declaration

- CSL – research + travel + support for student
- MSD – International Scientific Advisory Board + research + travel
- Hologic – support for research
- Sonic/DHM - support for research

# Objectives

To provide updates on:

- HPV and its related diseases
- Development in the elimination of HPV via vaccination programme internationally
- Local initiatives in HPV vaccination

# Structure

At the end of this session you should be able to:

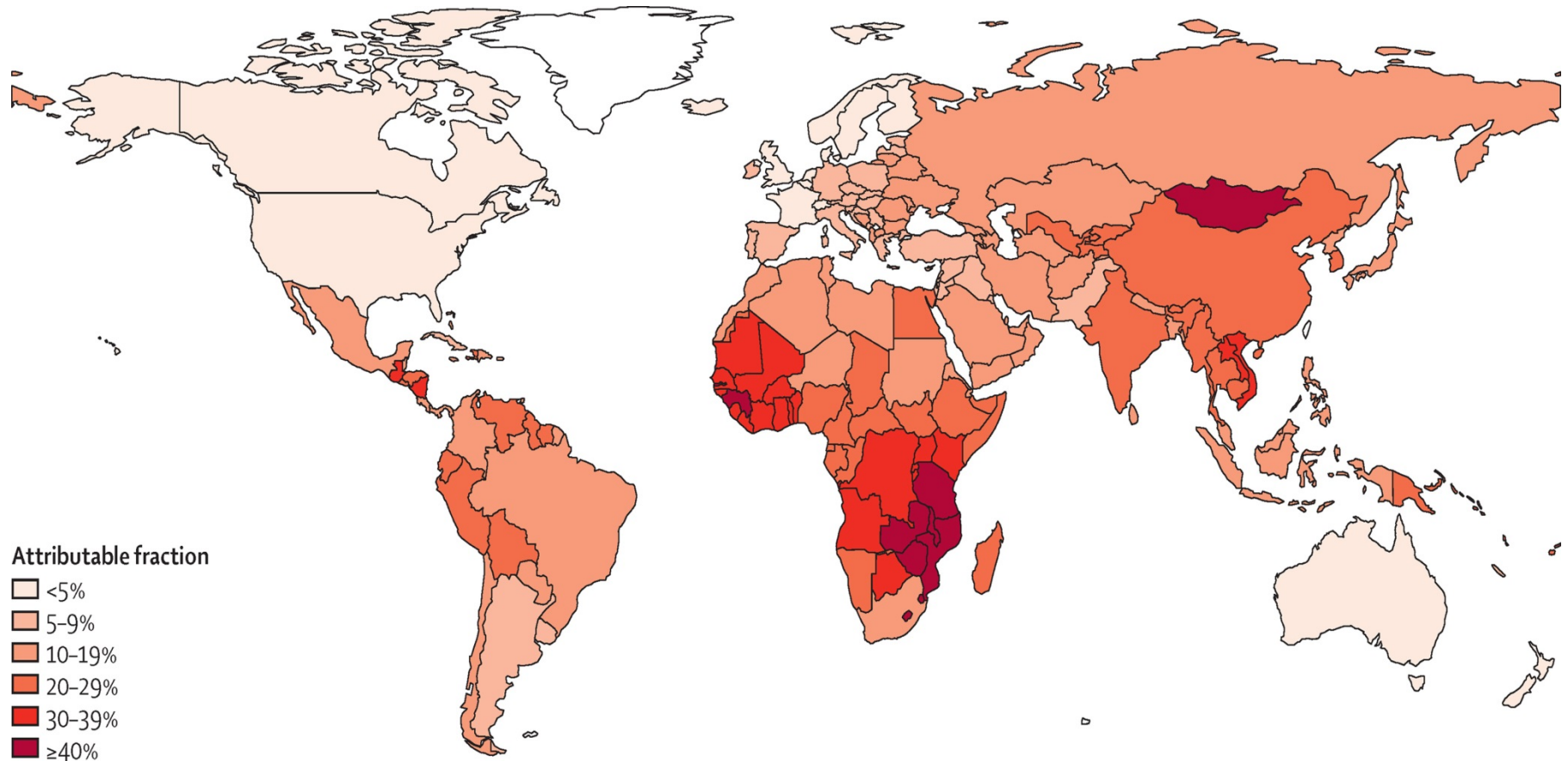
1. Understand the importance of HPV in human disease
2. Outline the basic virology and pathogenesis of HPV-related conditions
3. Describe the clinical characteristics and epidemiologies of the major HPV-related diseases
4. Evaluate current international progress towards the elimination of HPV
5. Discuss challenges to the implementation of elimination programs

# 1

## The importance of HPV

- Major human oncogen
- Responsible for  $\approx 500,000$  deaths annually
- “Benign” disease associated with disfiguring conditions & major economic implications
- Commonest STI
- Entirely preventable

# Global burden of cancers attributable to infections in 2012



# Infectious agents, by cancer type (International Classification of Diseases-10 code)

	Type of studies used for AF estimation	Laboratory method	Population and AF (95% CI)
<b><i>Helicobacter pylori</i>*</b>			
Non-cardia gastric carcinoma† (C16.1-9)	Cohort	Immunoblot	World: 89% (79-94)
Gastric cardia carcinoma† (C16.0)	Cohort	ELISA	East Asia: 29% (10-45)
Gastric non-Hodgkin lymphoma† (C82-85, C96)	Cohort and case-control	ELISA	World: 74% (43-86)
<b>Hepatitis B virus*</b>			
Liver cancer (C22)	Cohort, case-control, and case series	HBsAg	World: NS‡
<b>Hepatitis C virus*</b>			
Liver cancer (C22)	Cohort, case-control, and case series	ELISA (second or third generation)	World: NS‡
Non-Hodgkin lymphoma† (C82-85, C96)	Cohort and case-control	ELISA (second or third generation)	Low-risk countries: 1.7% (1.5-2.1) High-risk countries: 9.8% (8.2-12.0) Egypt: 24% (20-28)
<b>HPV (high-risk types)§</b>			
Cervix uteri carcinoma (C53)	Case-control	DNA PCR	World: 100%
Penile carcinoma† (C60)	Case-control	DNA PCR	World: 51% (47-55)
Anal carcinoma† (C21)	Case-control	DNA PCR with p16 <sup>INK4a</sup>	World: 88% (85-91)
Vulvar carcinoma† (C51)	Case-control	DNA PCR with p16 <sup>INK4a</sup>	Age 15-54 years: 48% (42-54) Age 55-64 years: 28% (23-33) Age ≥65 years: 15% (11-18)
Vaginal carcinoma† (C52)	Case-control	DNA PCR	World: 78% (68-86)
Carcinoma of the oropharynx, including tonsils and base of tongue† (C01, C09-10)	Case-control	PCR for DNA and HPV E6/E7 mRNA expression	North America: 51% (41-57) Northwest Europe: 42% (34-47) East Europe: 50% (39-57) South Europe: 24% (17-30) China: 23% (17-27) Japan: 46% (39-53) India: 22% (5-44) South Korea: 60% (46-70) Australia: 41% (32-47) Elsewhere: 13% (5-23)
Cancer of the oral cavity† (C02-06)	Case-control	PCR for DNA and HPV E6/E7 mRNA expression	World: 4.3% (3.2-5.7)
Laryngeal cancer (C32)	Case-control	PCR for DNA and HPV E6/E7 mRNA expression	World: 4.6% (3.3-6.1)
<b>EBV §</b>			
Hodgkin's lymphoma (C81)	Cohort and case-control	In-situ hybridisation of EBV-encoded small RNAs and EBV latent membrane protein 1	Africa: 74% (65-82) Latin America: 60% (54-67) Asia: 56% (52-60) Europe: 36% (32-39) North America: 32% (25-39) Australia: 29% (10-58)
Burkitt's lymphoma† (C83.7)	Case-control and case series	In-situ hybridisation of EBV-encoded small RNAs and Epstein-Barr nuclear antigen 4	Sub-Saharan Africa: 100% USA and Europe: 20% Elsewhere: 30%
Nasopharyngeal carcinoma (C11)	Case-control and case series	In-situ hybridisation of EBV-encoded small RNAs	High-incidence countries: 100% Low-incidence countries: 80%
<b>Human herpesvirus type 8§</b>			
Kaposi's sarcoma (C46)	Not applicable	DNA PCR	World: 100%
<b>Human T-cell lymphotropic virus*</b>			
Adult T-cell leukaemia and lymphoma† (C91.5)	Not applicable	Immunoblot	World: 100%
<b><i>Opisthorchis viverrini</i> and <i>Clonorchis sinensis</i></b>			
Bile duct cancer† (C22.1)	Case-control	Various	Endemic areas in southeast Asia: NM¶
<b><i>Schistosoma haematobium</i></b>			
Bladder carcinoma (C67)	Case-control	Various	Endemic areas in Africa: 41% (36-48)

AF: attributable fraction. HPV: human papillomavirus. EBV: Epstein-Barr virus. \* In sera. † These subtypes were not directly available in GLOBOCAN 2012; therefore, data from the Cancer Incidence in Five Continents (CIS X) database were used to estimate the corresponding incidence. ‡ NS: not shown because country-specific estimates were used (appendix). § In cancer tissue. ¶ NA: not available because a different method was used to calculate AF.

Table 1: General methods for the calculation of the AFs of infectious agents, by cancer type (International Classification of Diseases-10 code)



## Site of cancer

## Proportion attributed to high risk HPV

Cervix uteri carcinoma (C53)

World: 100%

Penile carcinoma† (C60)

World: 51% (47–55)

Anal carcinoma† (C21)

World: 88% (85–91)

Vulvar carcinoma† (C51)

Age 15–54 years: 48% (42–54)

Age 55–64 years: 28% (23–33)

Age ≥65 years: 15% (11–18)

Vaginal carcinoma† (C52)

World: 78% (68–86)

Carcinoma of the oropharynx, including tonsil and base of tongue† (C01, C09–10)

North America: 51% (41–57)

Northwest Europe: 42% (34–47)

East Europe: 50% (39–57)

South Europe: 24% (17–30)

China: 23% (17–27)

Japan: 46% (39–59)

India: 22% (5–44)

South Korea: 60% (46–70)

Australia: 41% (32–47)

Elsewhere: 13% (5–23)

Cancer of the oral cavity† (C02–06)

World: 4.3% (3.2–5.7)

Laryngeal cancer (C32)

World: 4.6% (3.3–6.1)

## Attributable Fractions of infectious agents, by cancer type



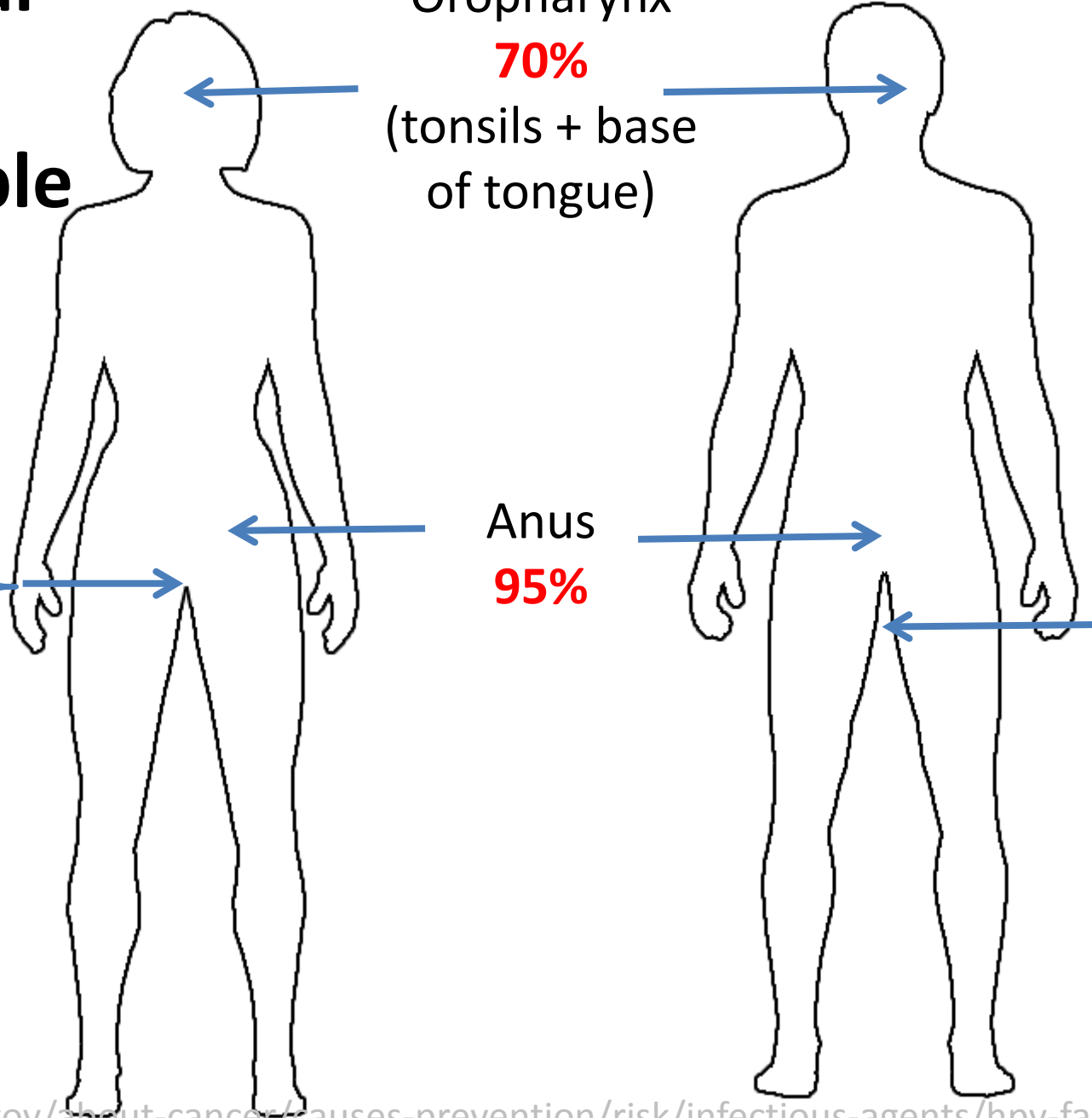
# 5% global cancers attributable to HPV

Oropharynx  
**70%**  
(tonsils + base  
of tongue)

Cervix - **100%**  
Vagina - **65%**  
Vulva - **50%**

Anus  
**95%**

Penis  
**35%**





# Selected cancers in Hong Kong (2015)

## Site

Lip, oral cavity and  
pharynx, (except NP)

Cervix

Vag/Vul/other female  
gen

Penis

Rectum/anus

Colon

Nasopharynx

# Selected cancers in Hong Kong (2015)

Site	ASR
Lip, oral cavity and pharynx, (except NP)	4.7
Cervix	7.6
Vag/Vul/other female gen	1.0
Penis	(0.5)
Rectum/anus	13.9
Colon	19.7
Nasopharynx	7.5

# Selected cancers in Hong Kong (2015)

Site	ASR	Number
Lip, oral cavity and pharynx, (except NP)	4.7	628
Cervix	7.6	500
Vag/Vul/other female gen	1.0	85
Penis	(0.5)	35
Rectum/anus	13.9	1992
Colon	19.7	3044
Nasopharynx	7.5	1504

# Selected cancers in Hong Kong (2015)

Site	ASR	Number	%HPV
Lip, oral cavity and pharynx, (except NP)	4.7	628	70%
Cervix	7.6	500	100%
Vag/Vul/other female gen	1.0	85	60%
Penis	(0.5)	35	35%
Rectum/anus	13.9	1992	? (95%)
Colon	19.7	3044	-
Nasopharynx	7.5	1504	-



# Selected cancers in Hong Kong (2015)

Site	ASR	Number	%HPV	n = HPV
Lip, oral cavity and pharynx, (except NP)	4.7	628	70%	440
Cervix	7.6	500	100%	500
Vag/Vul/other female gen	1.0	85	60%	51
Penis	(0.5)	35	35%	12
Rectum/anus	13.9	1992	? (95%)	?
Colon	19.7	3044	-	-
Nasopharynx	7.5	1504	-	-



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				<b>≥1003</b>





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Colon	19.7	3044	-	-
Nasopharynx	7.5	1504	-	-
				<b>≥1003</b>

2015: 835 new  
HIV/AIDS



News / Hong Kong / HEALTH

## Hongkongers' lifestyles to blame for 18pc rise in cancer deaths over decade

Hospital data shows number of patients has risen by 27 per cent over last decade

PUBLISHED : Wednesday, 04 February, 2015, 3:24am

UPDATED : Wednesday, 04 February, 2015, 6:51pm

COMMENTS: 18

### MOST POPULAR

VIEWED

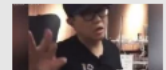
SHARED

COMMENTED

1 Kim Jong-un due to arrive in Singapore on Sunday afternoon



2 'Please just go': Chinese tourists asked



**2**

# **Virology & pathogenesis**

# Virology of HPV

Icosahedral capsule



HPV = 55nm



[www.shutterstock.com](http://www.shutterstock.com) · 211430561

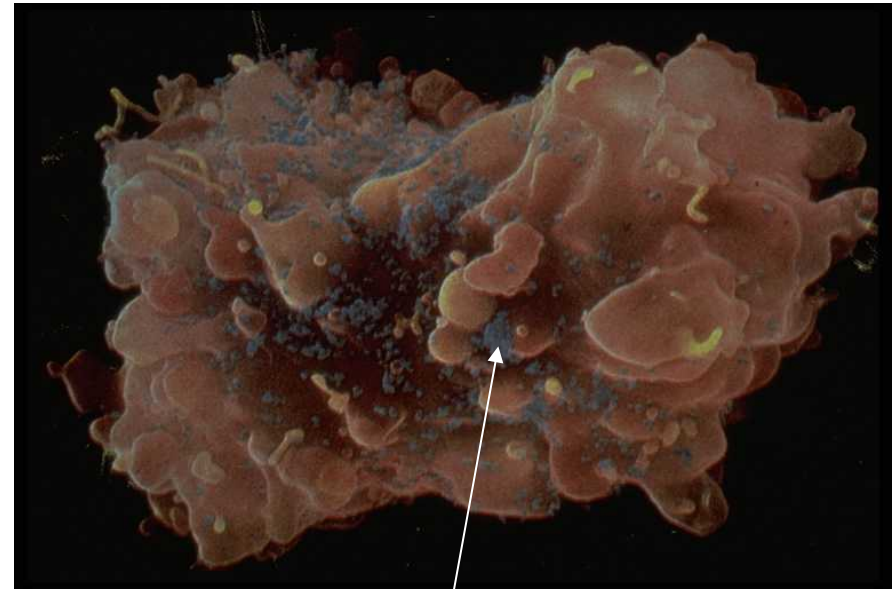
Circular, double stranded DNA  $\approx$   
8000bp

# Virology of HPV



HPV = 55nm

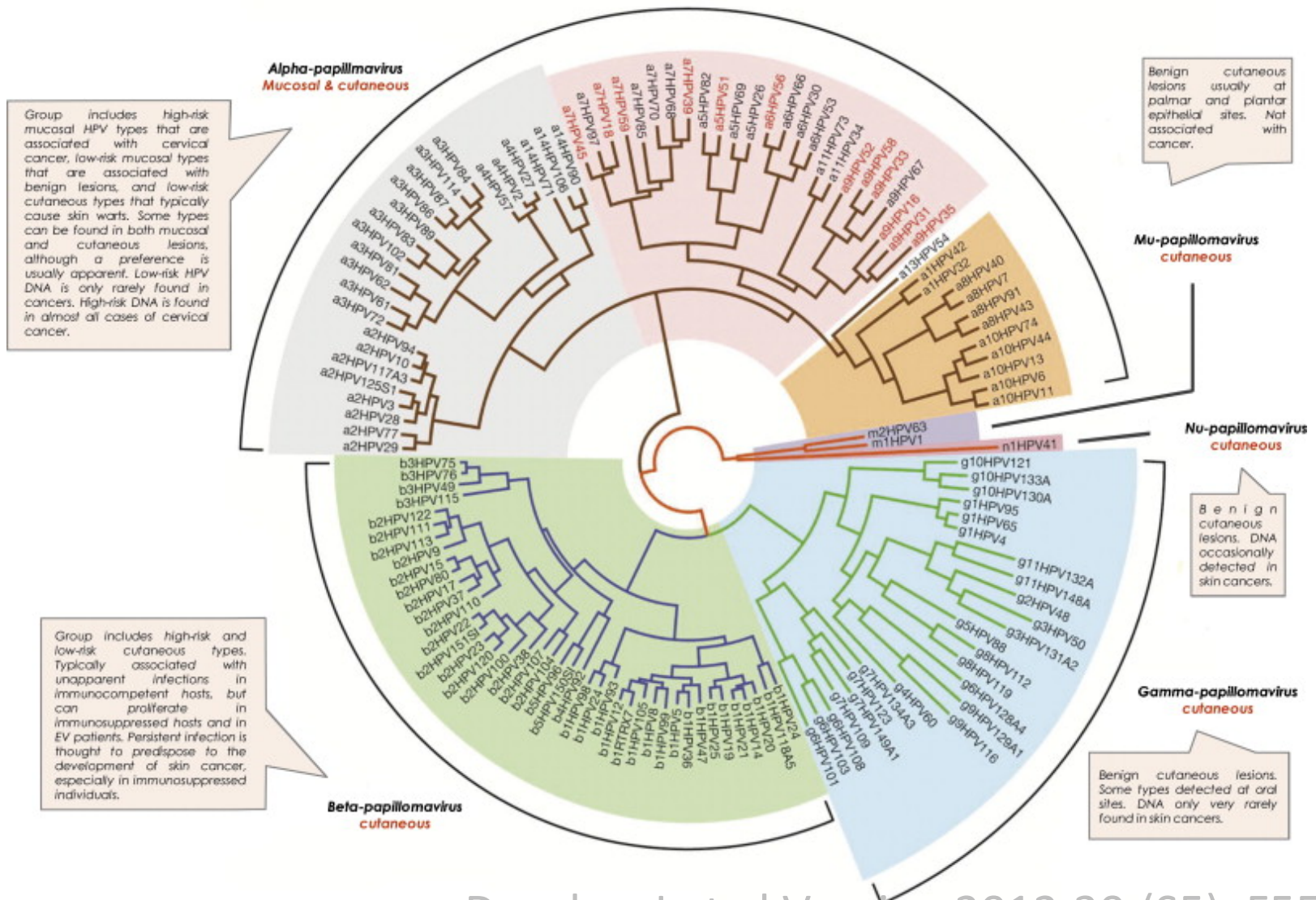
Human Papillomavirus (HPV)



HIV = 100nm

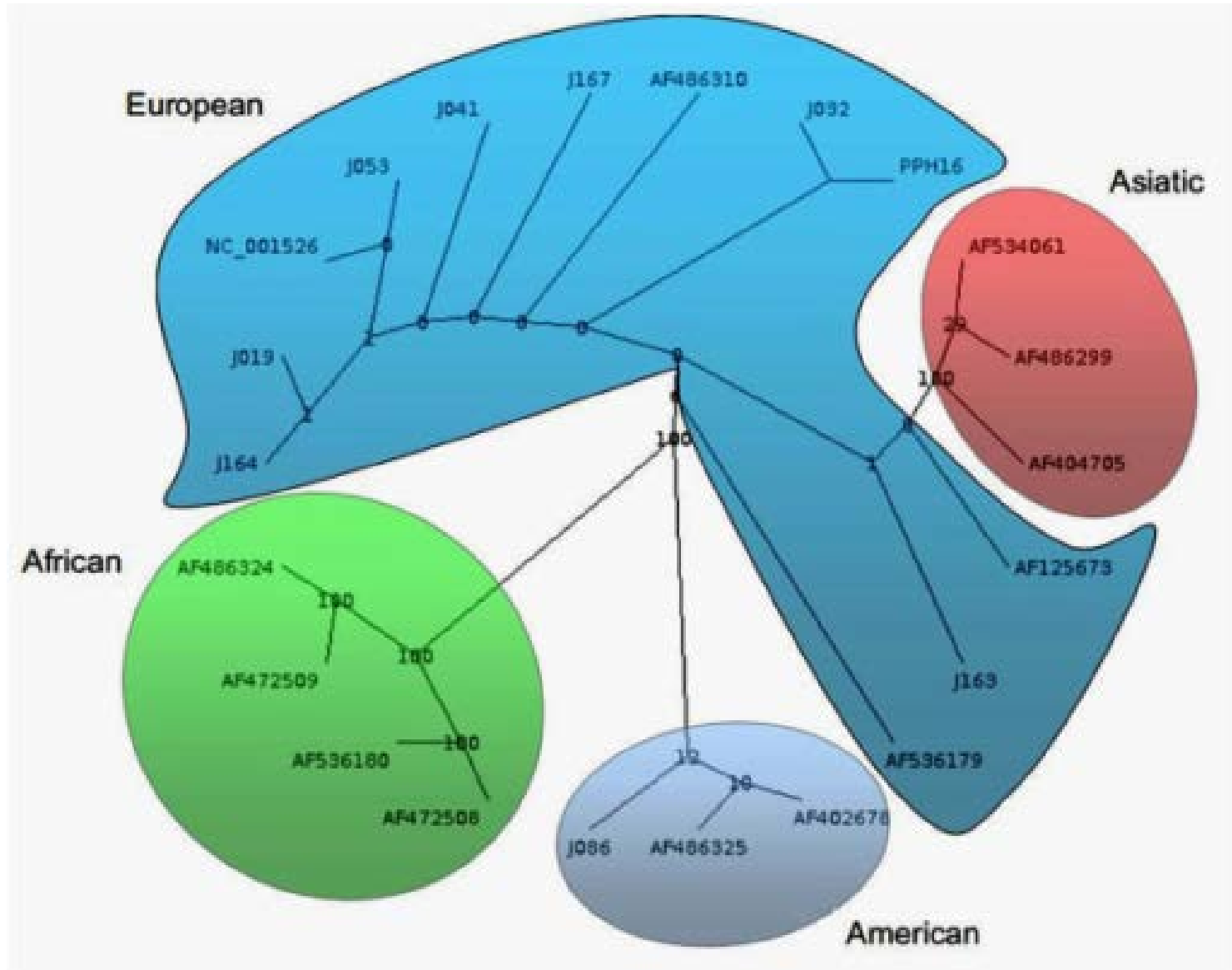
Human Immunodeficiency Virus  
(HIV) on a T cell

# There are many types of HPV



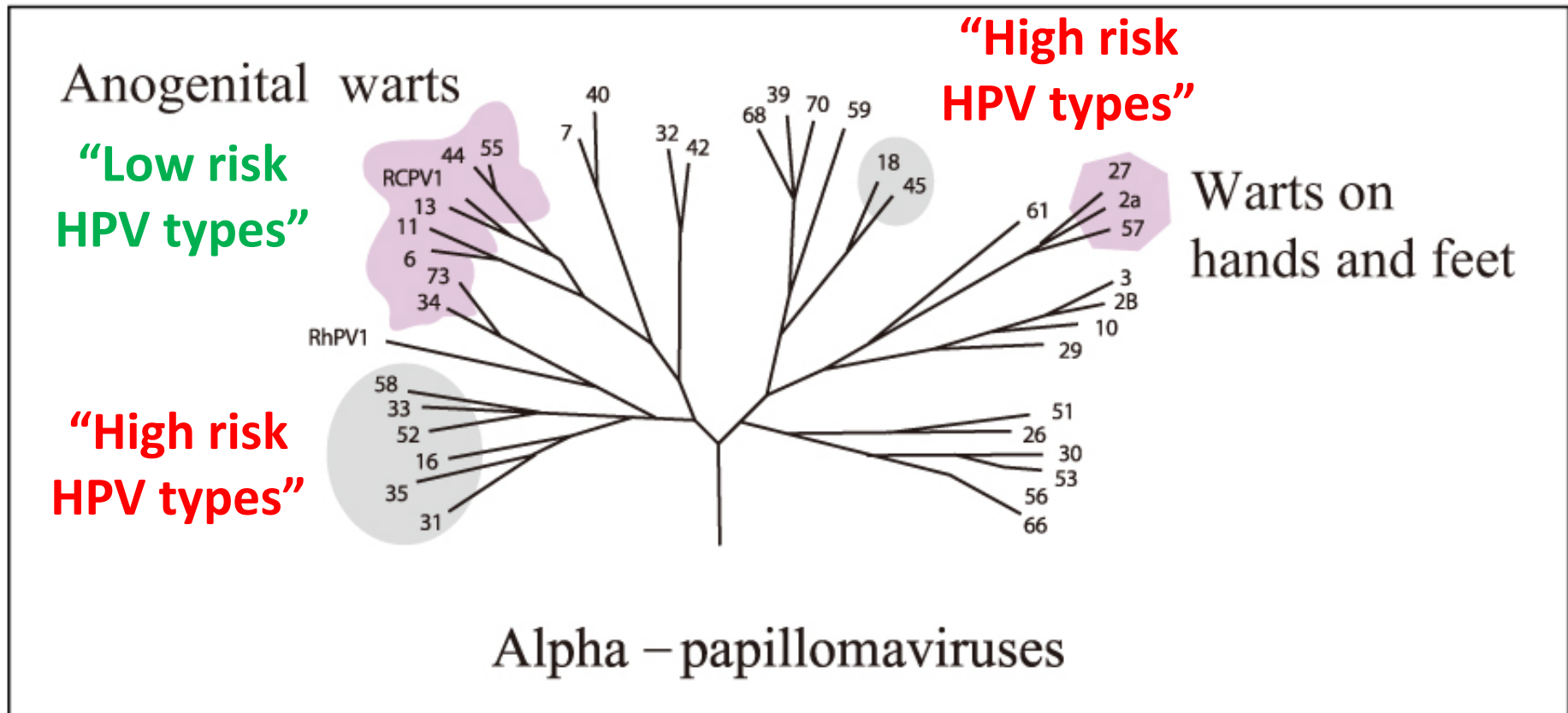


# HPV-16 phylogenetic tree based on **E6** sequencing

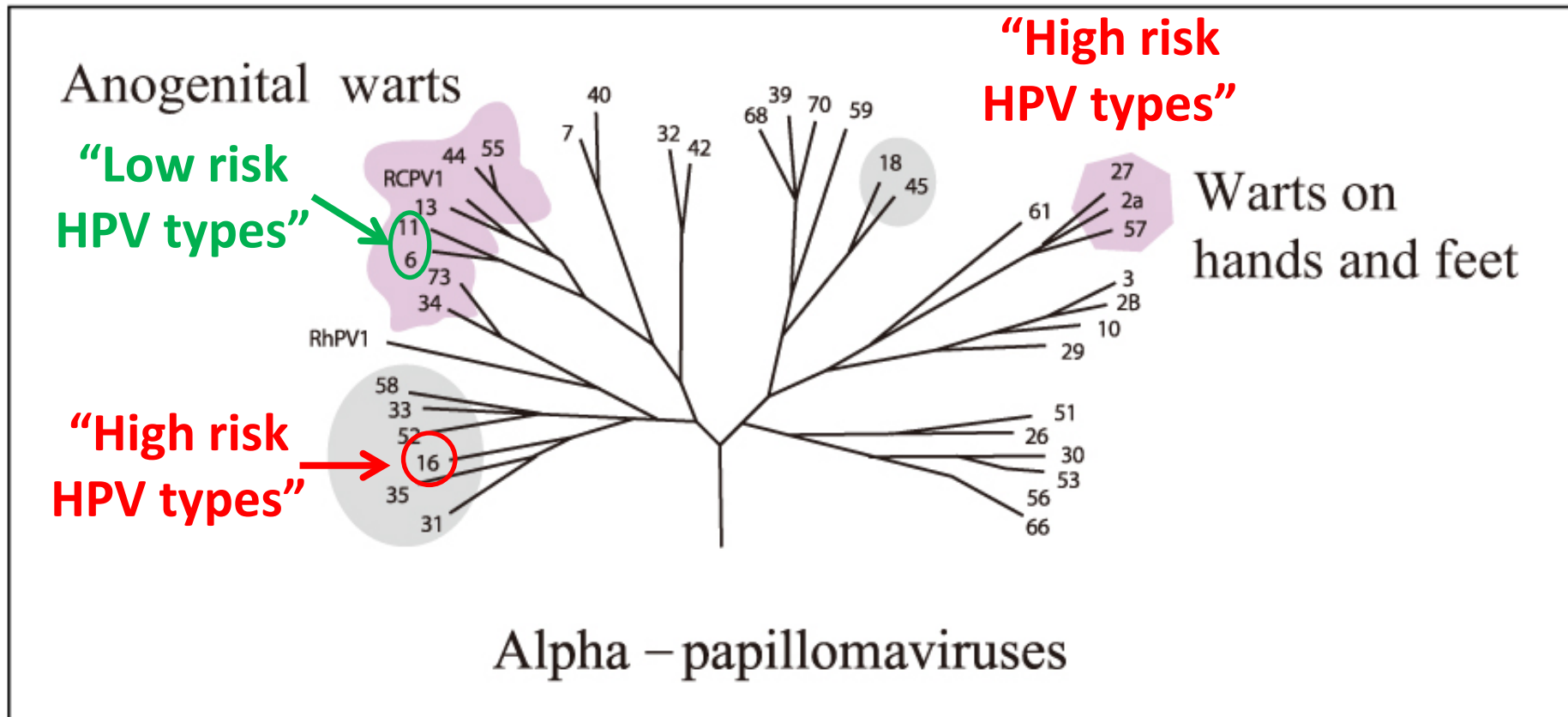




# Simplified phylogenetic tree (L1)



# Simplified phylogenetic tree (L1)



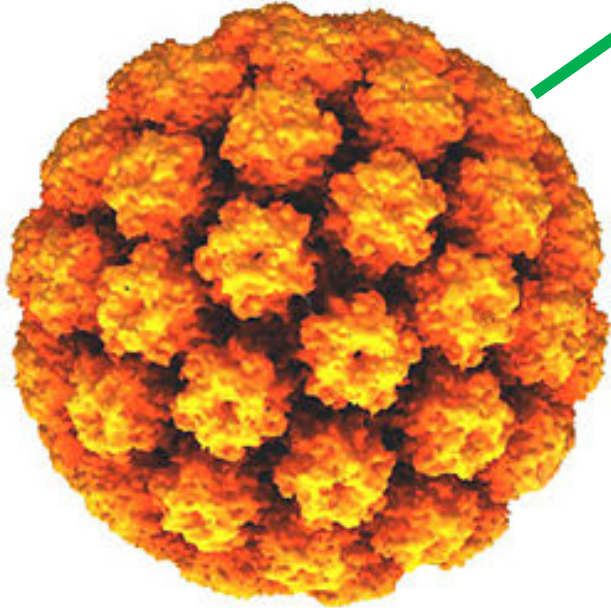
HPV types 6 & 11 = Low risk

HPV type 16 = High risk

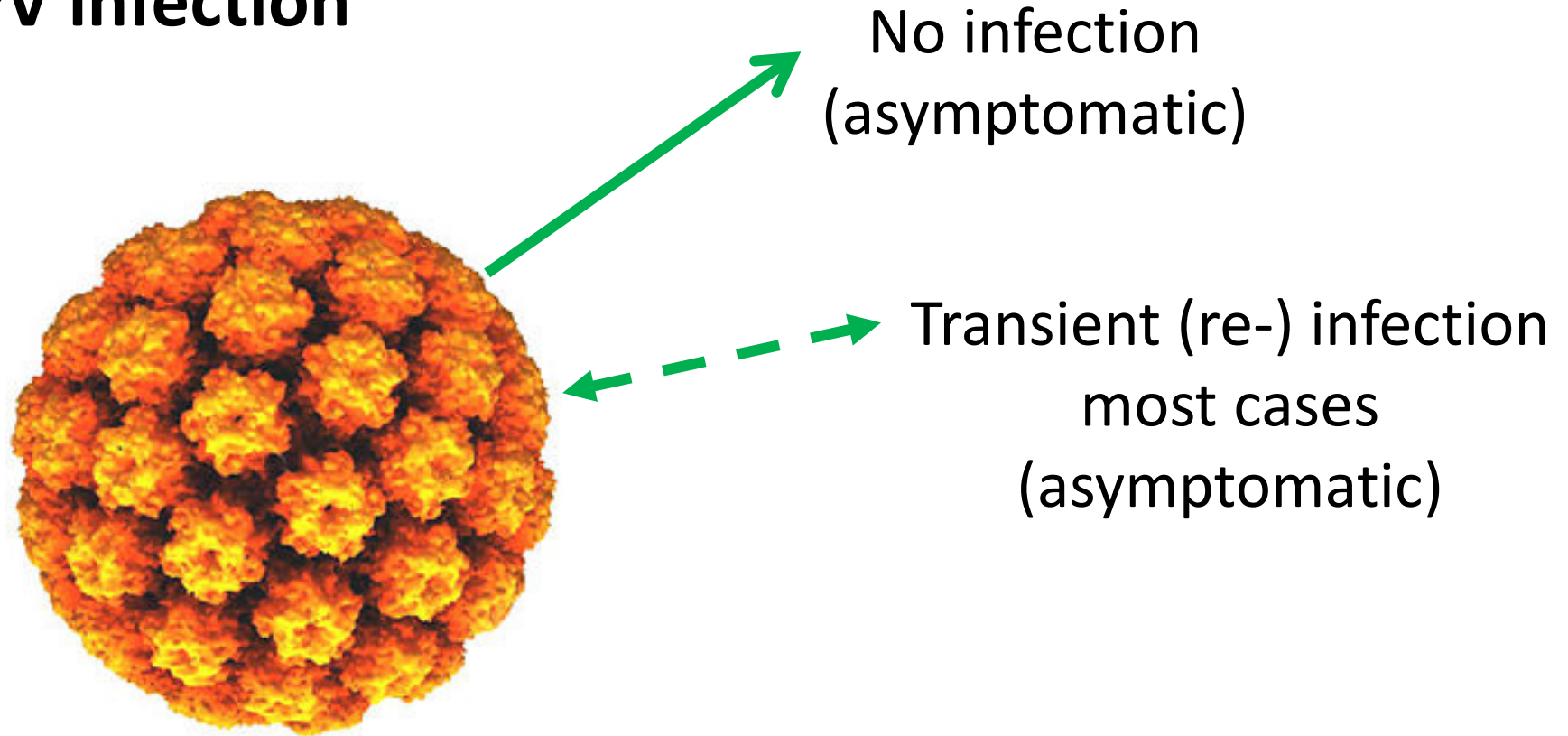
# **Infection with HPV**

# Potential outcomes of HPV infection

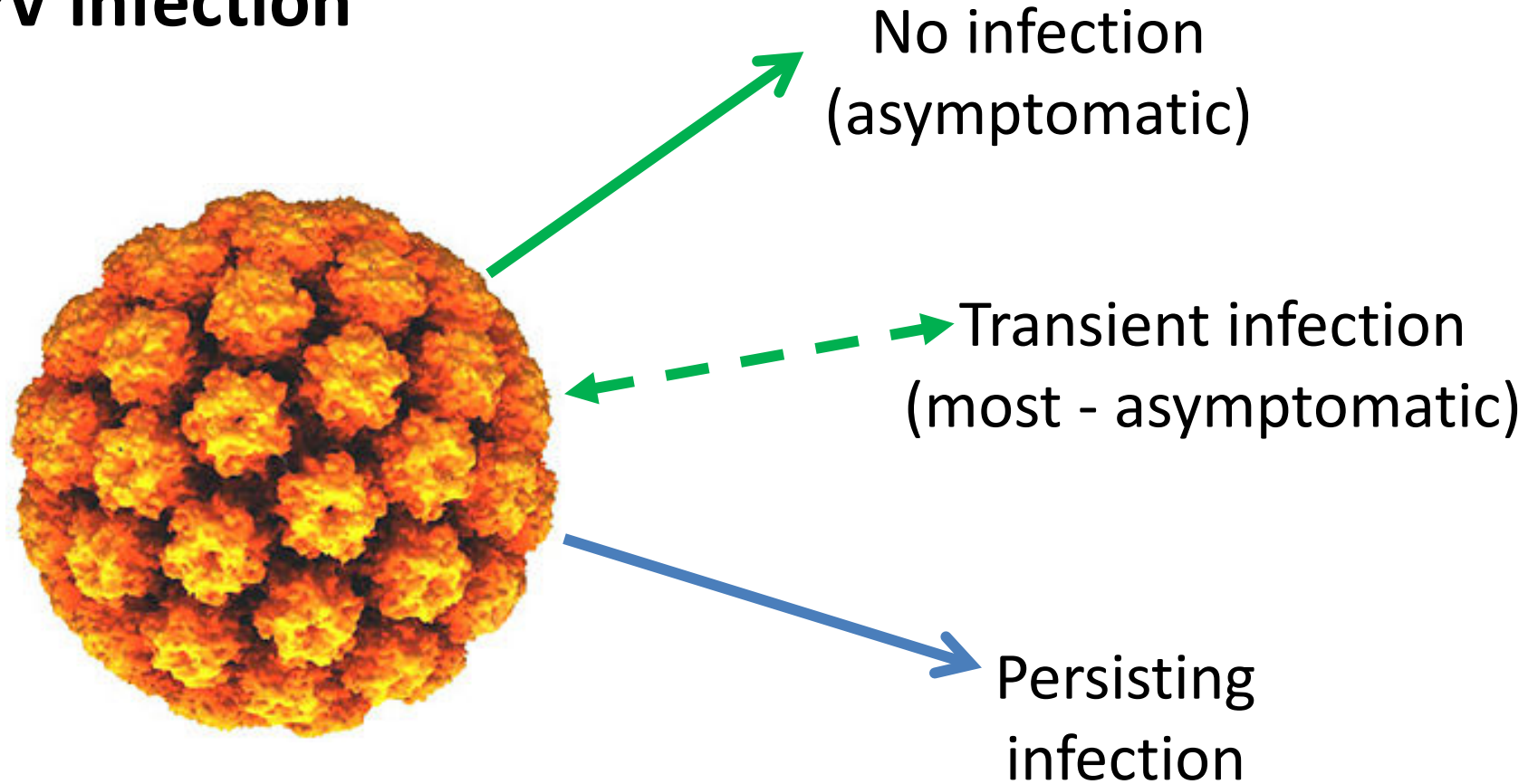
No infection  
(asymptomatic)



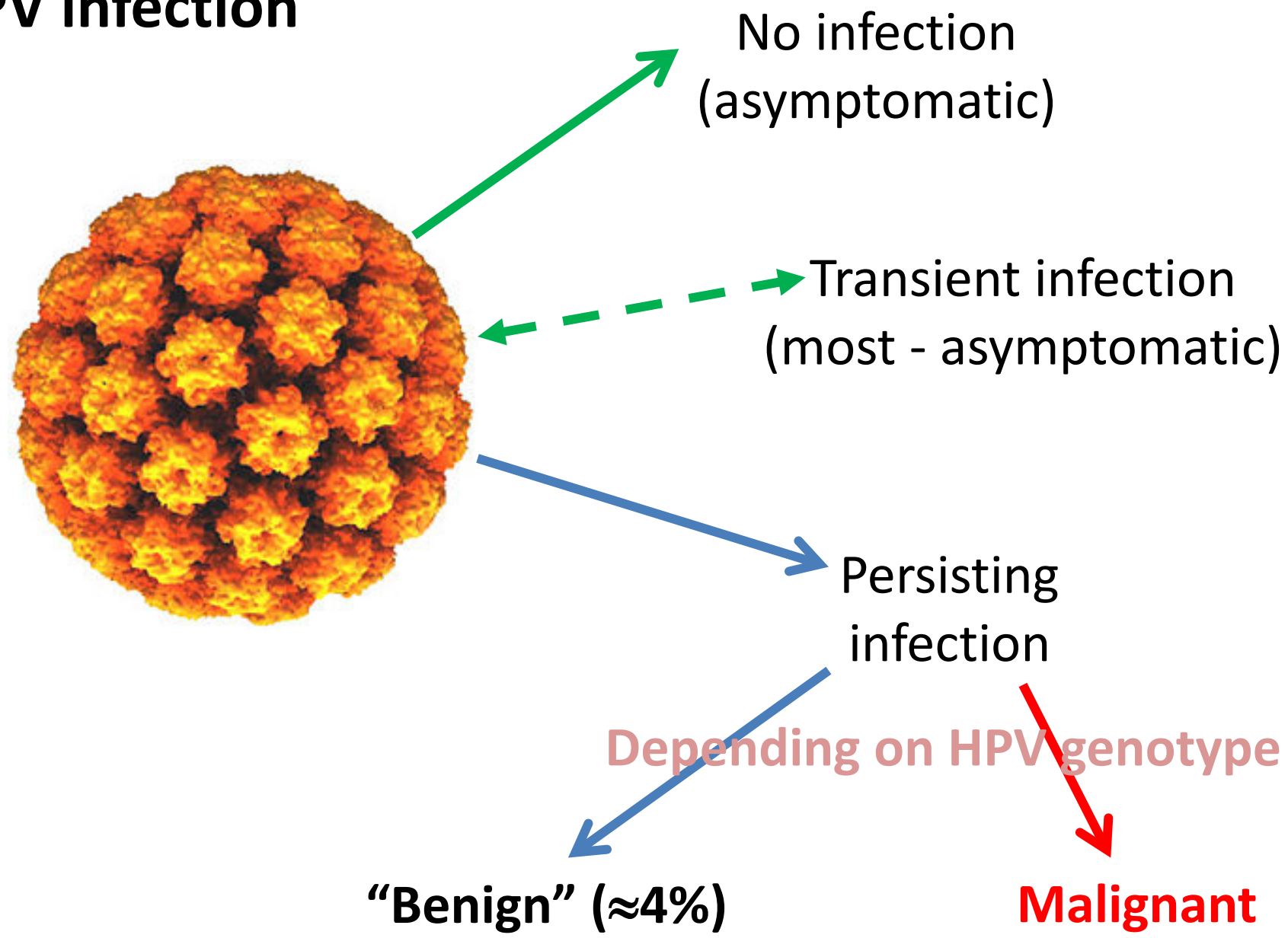
# Potential outcomes of HPV infection



# Potential outcomes of HPV infection

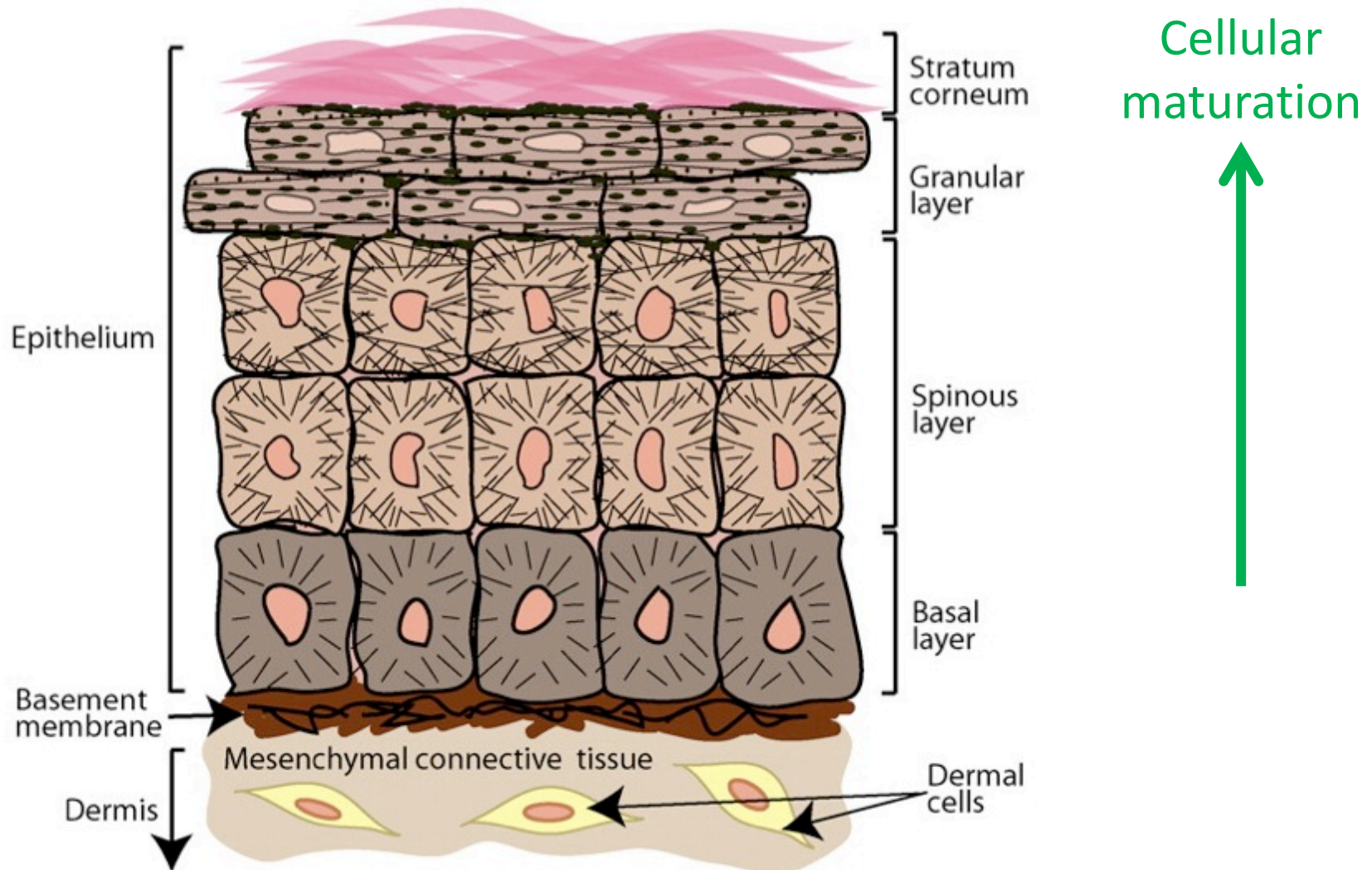


# Potential outcomes of HPV infection

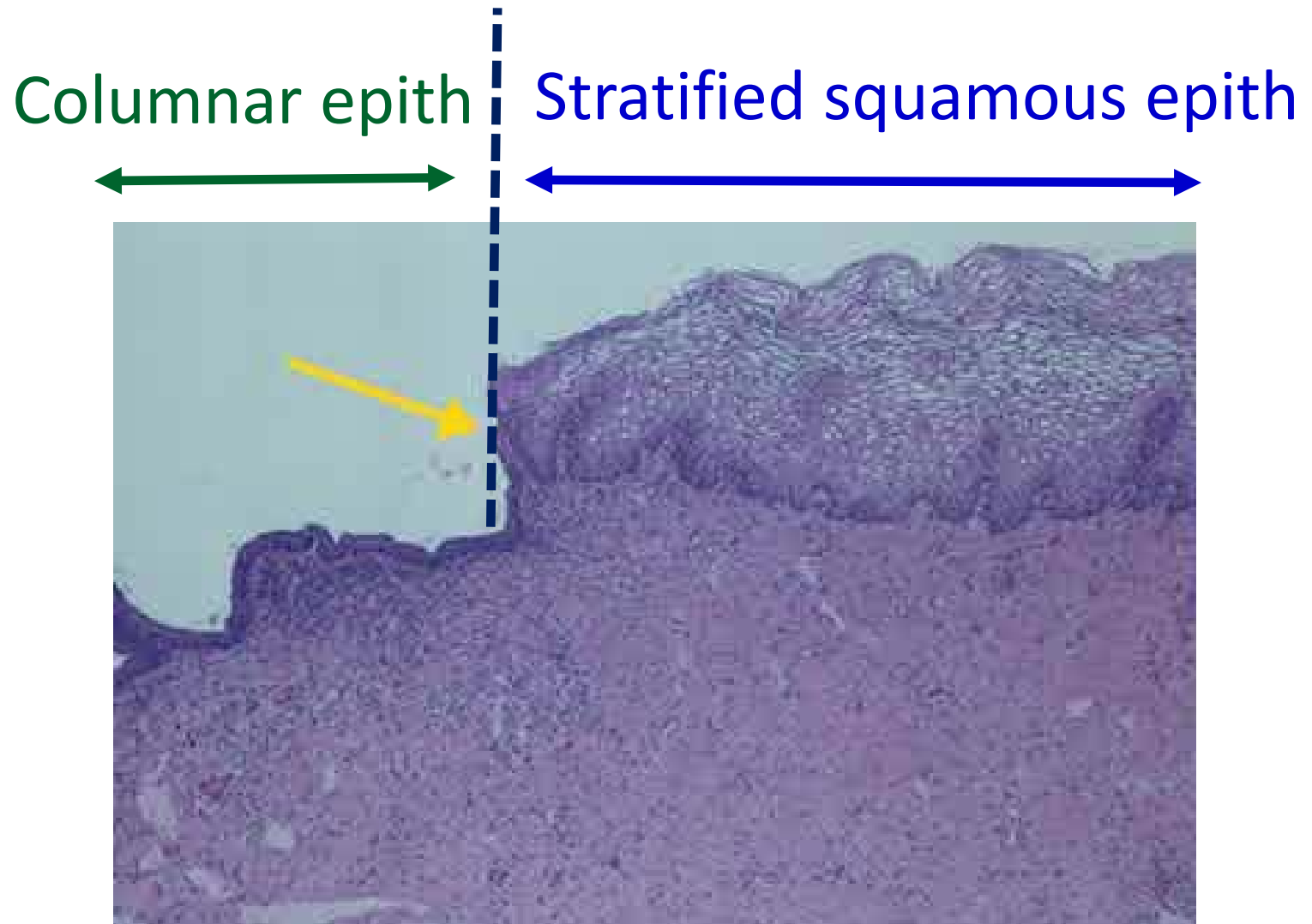




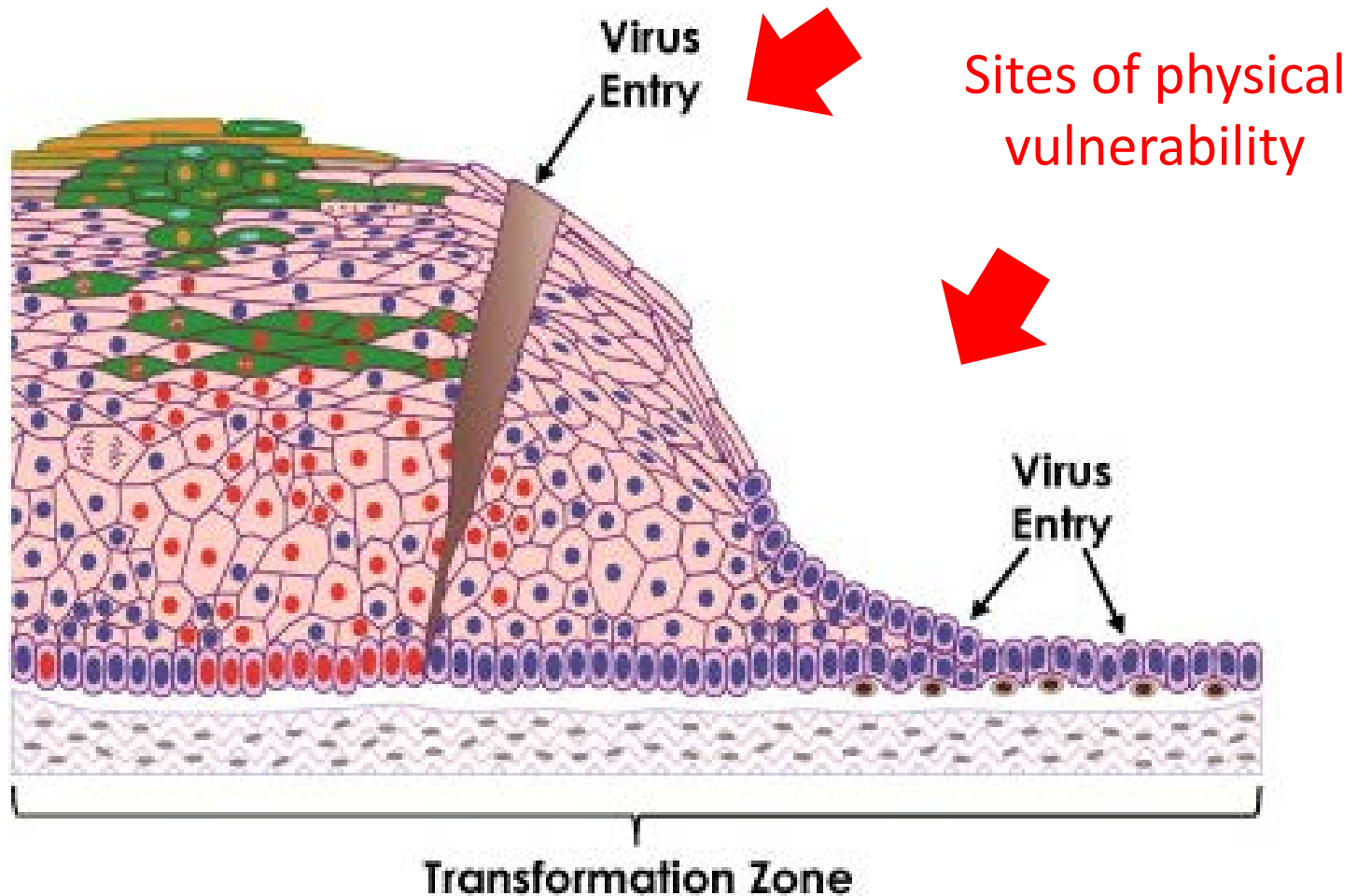
# Normal skin structure



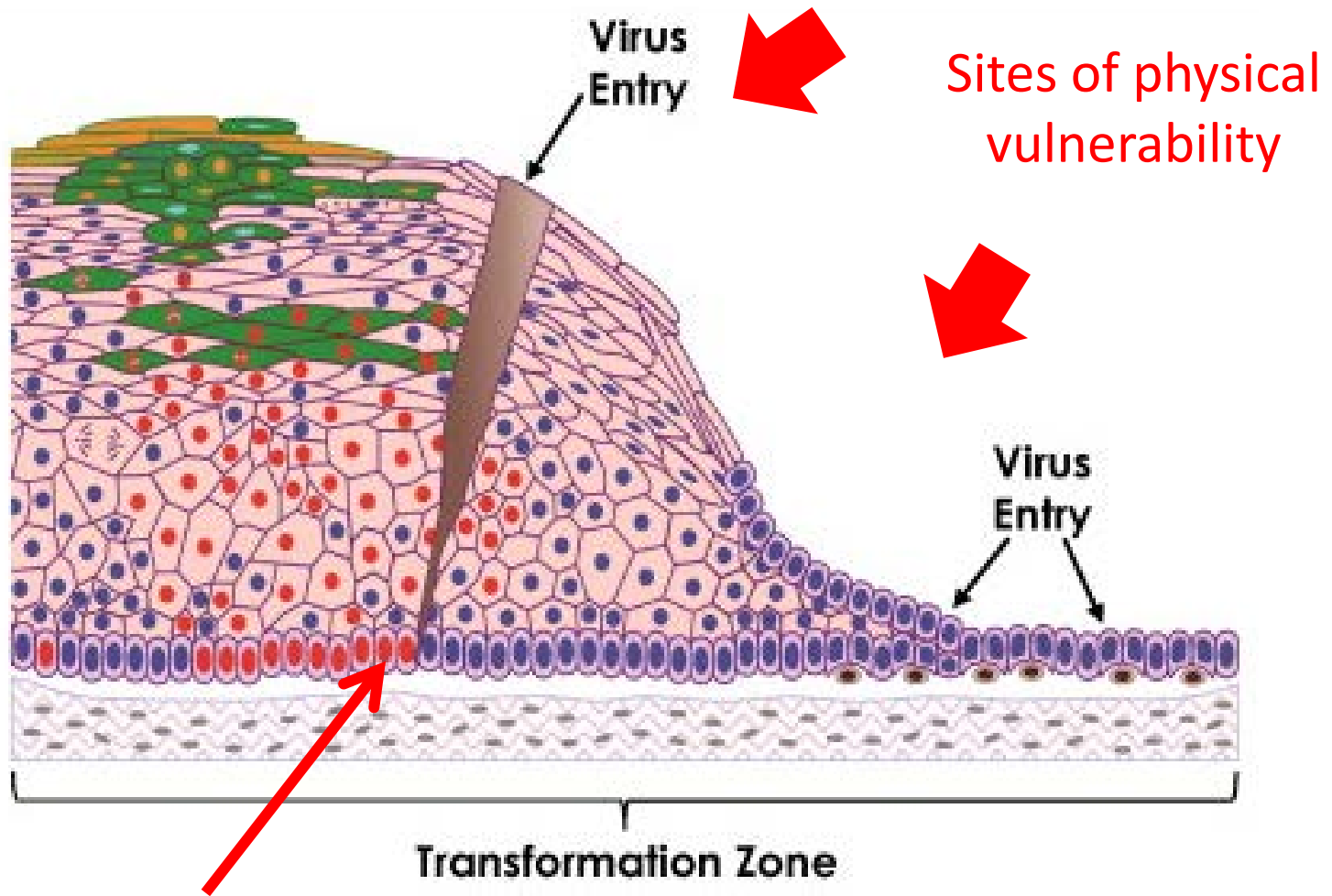
# Cervical squamo-columnar junction



# Viral processes in HPV infection

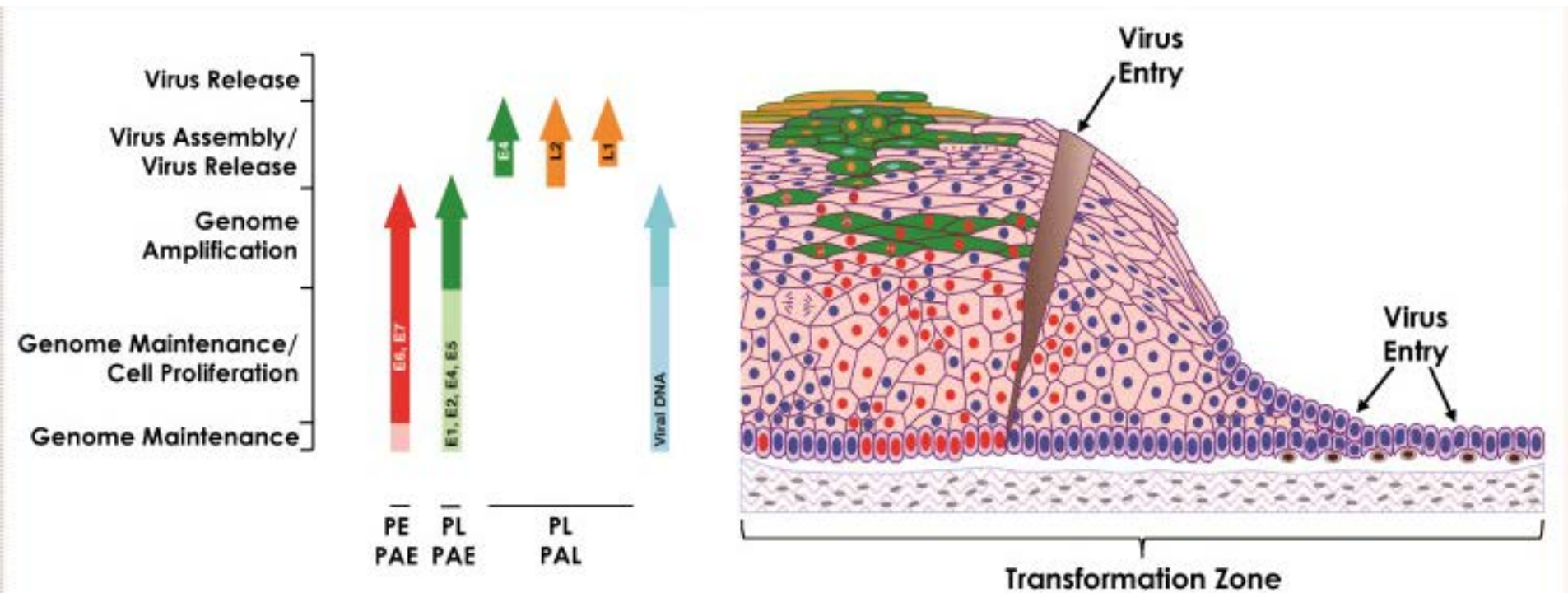


# Viral processes in HPV infection



Only **basal cells** are permissive of infection

# Viral processes in HPV infection



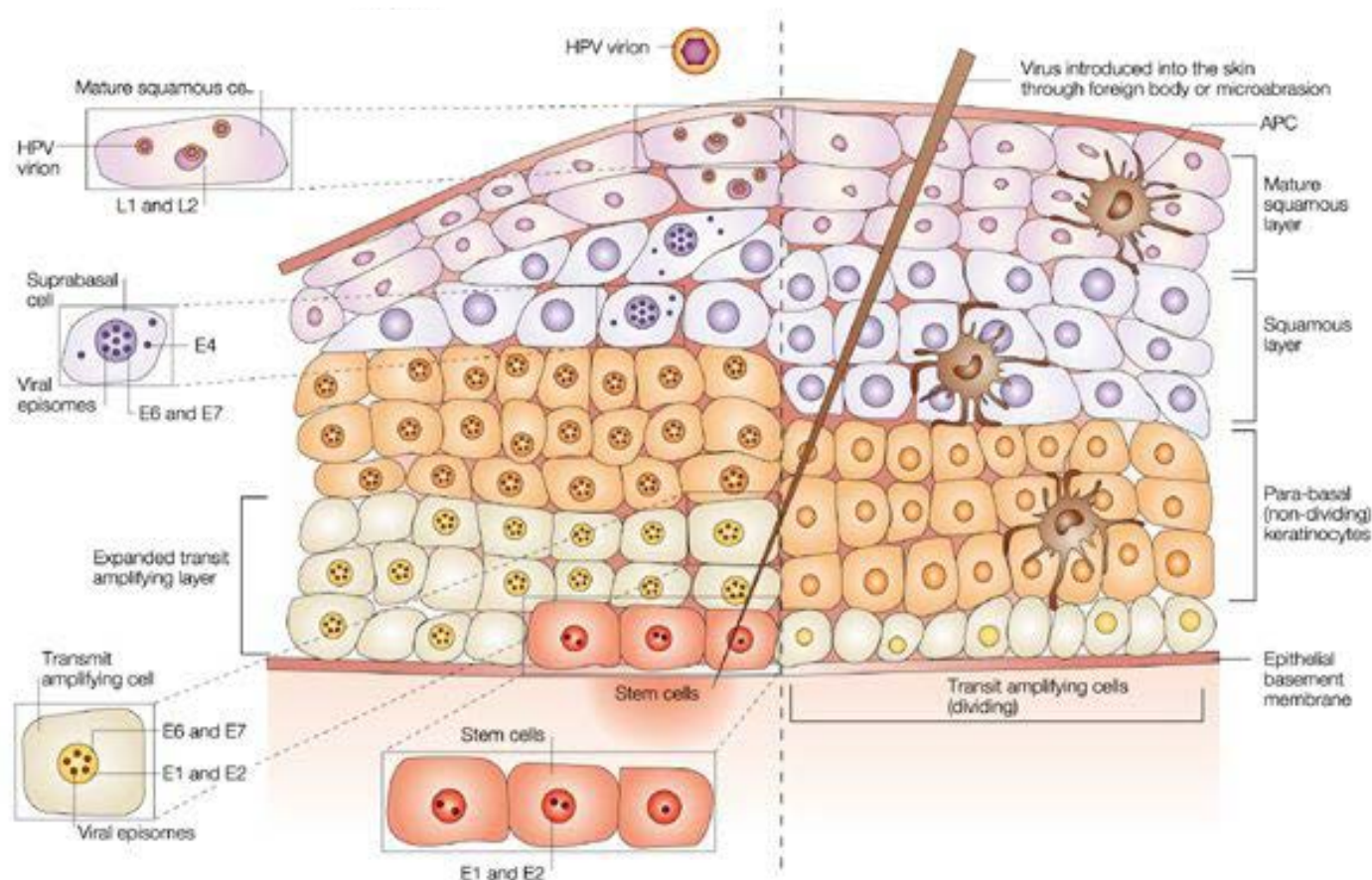
HPV-induced cellular changes  
ascend through epithelium  
(effects depend on HPV type)



# Immunological processes in HPV infection

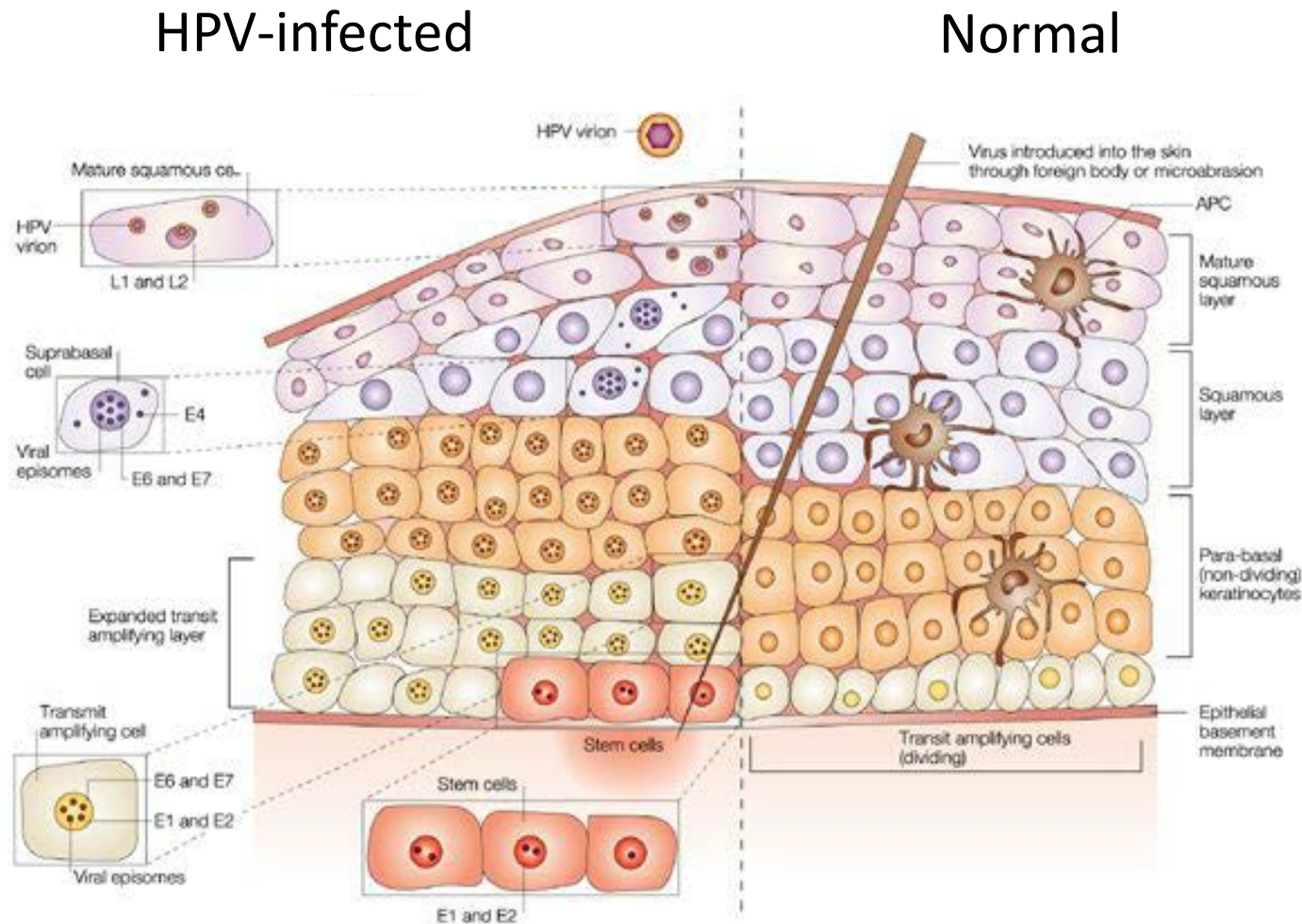
HPV-infected

Normal



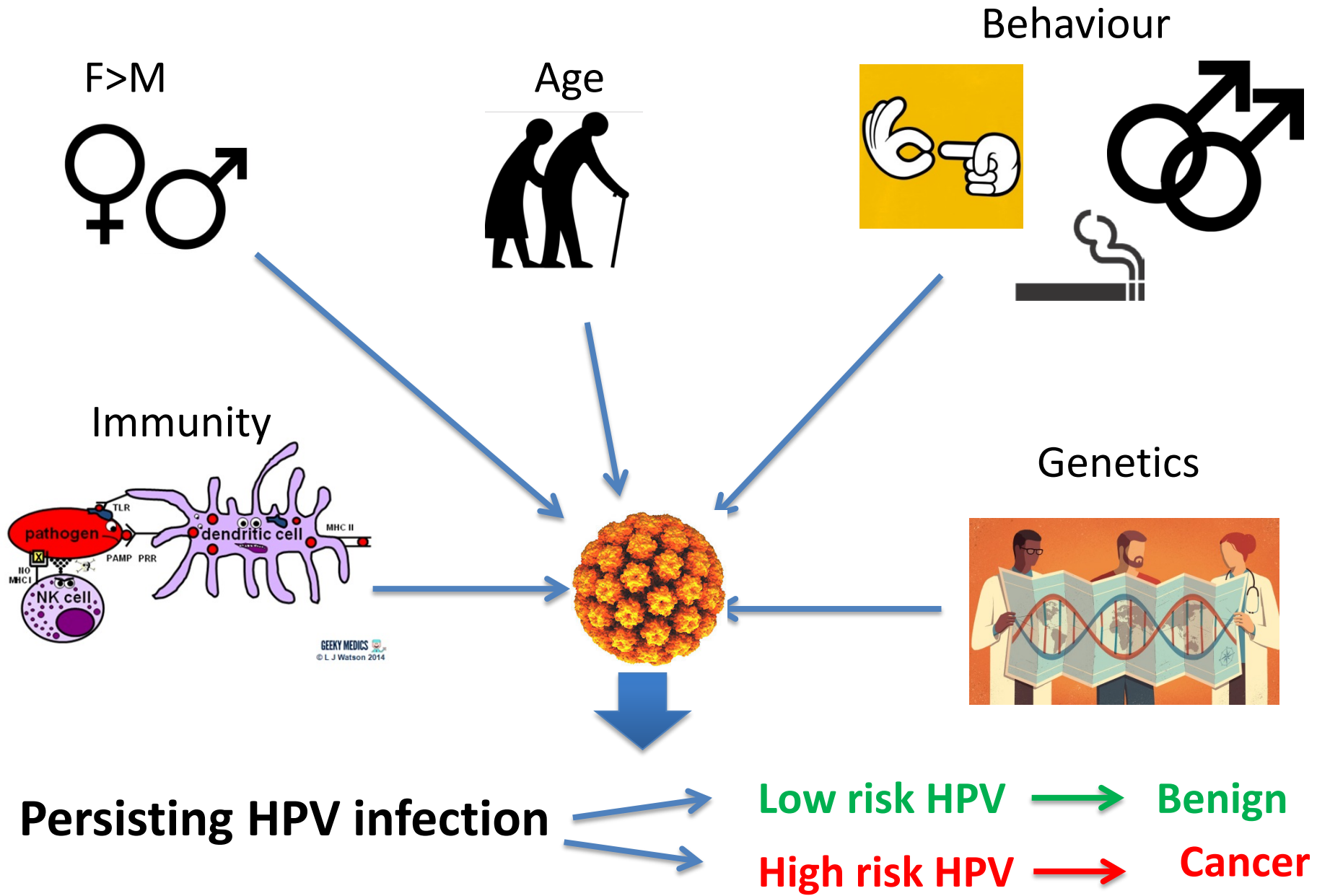
# Immunological processes in HPV infection

HPV-infected cells become “invisible” to the immune system

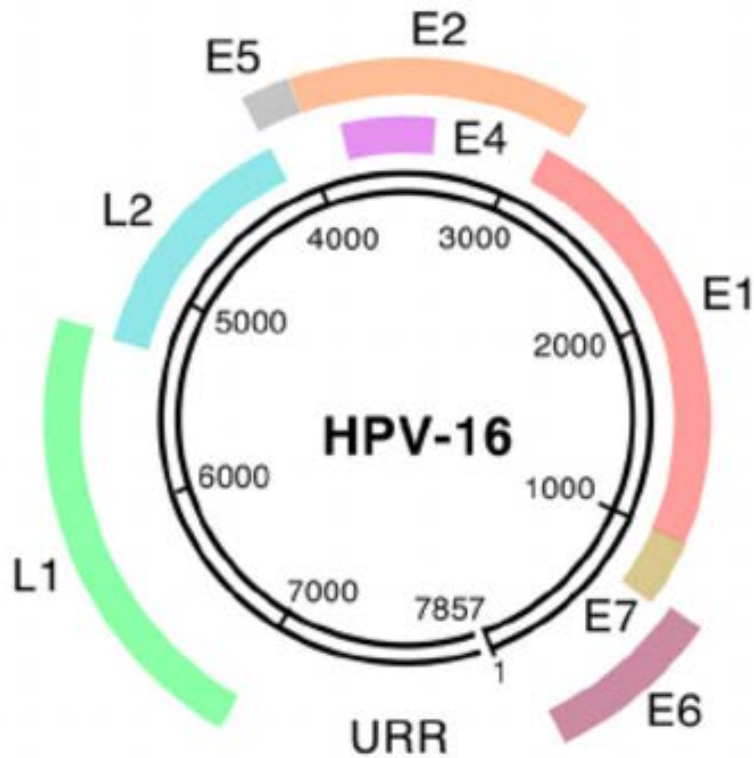




# Risk factors for HPV-associated cancers

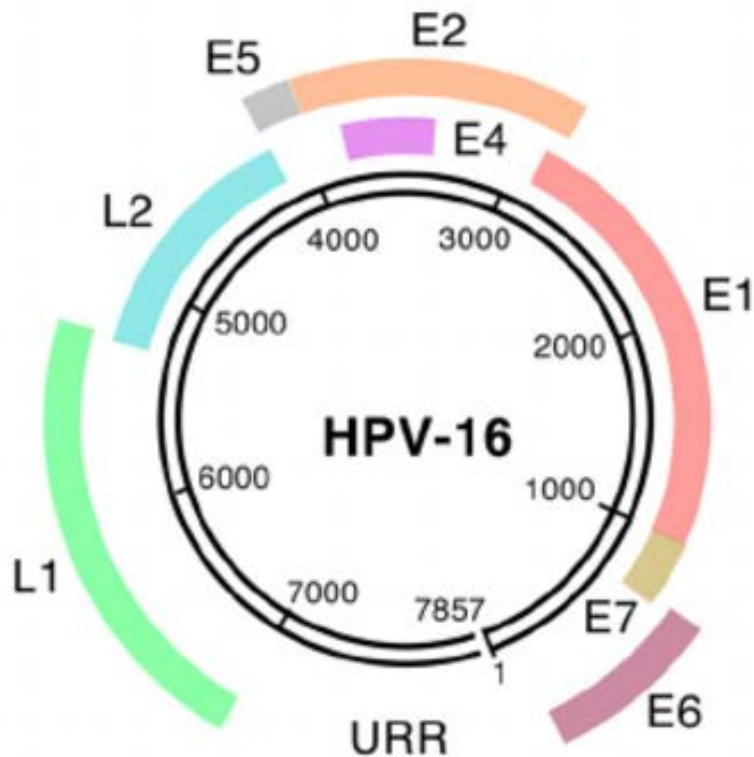


# HPV-16 genome

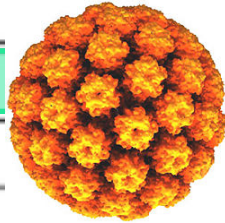


Gene	Function
L1	Major capsid protein.
L2	Minor capsid protein.
E1	Transcription factor, helicase activity. Mediates episomal DNA replication.
E2	Transcription factor. Regulates viral copy number.
E4	Facilitates virion release.
E5	Stimulates cell proliferation and prevents differentiation. Downregulates surface MHC class I expression.
E6	Deregulates cell cycle control through p53 inactivation/degradation. Induces malignant transformation together with E7.
E7	Keeps cells active in the cell cycle through Rb inactivation. Induces malignant transformation alone and together with E6.

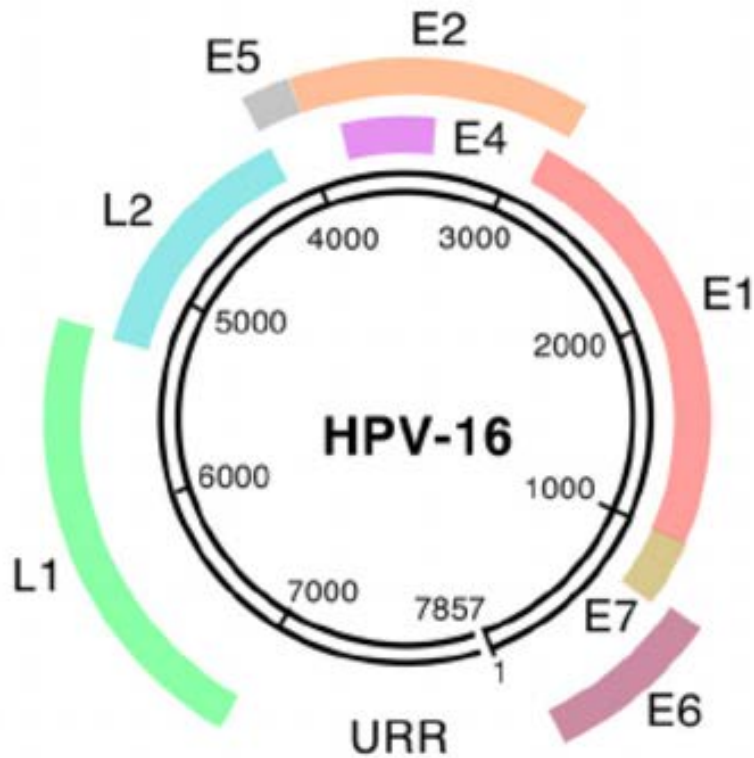
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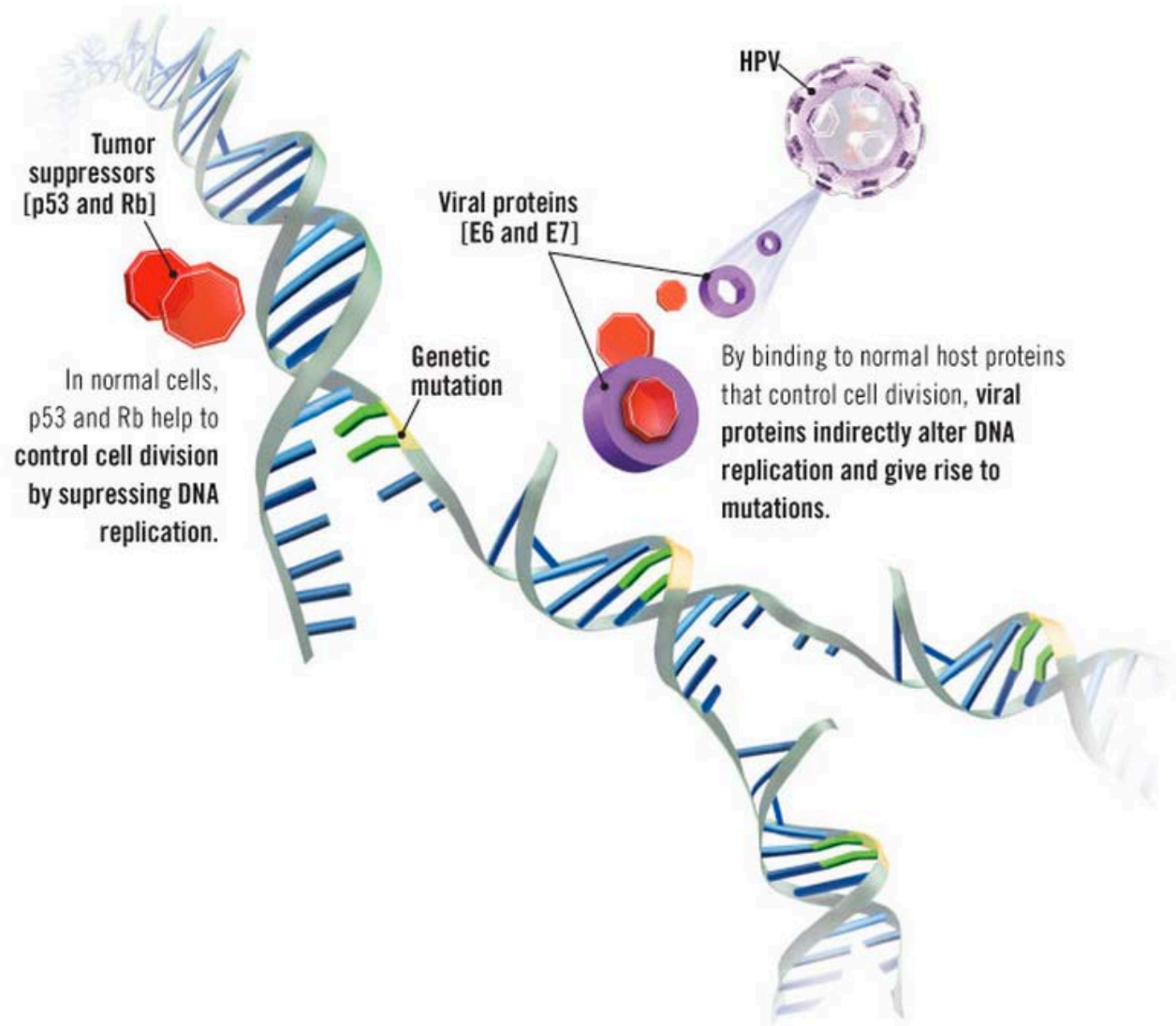


# HPV-16 genome



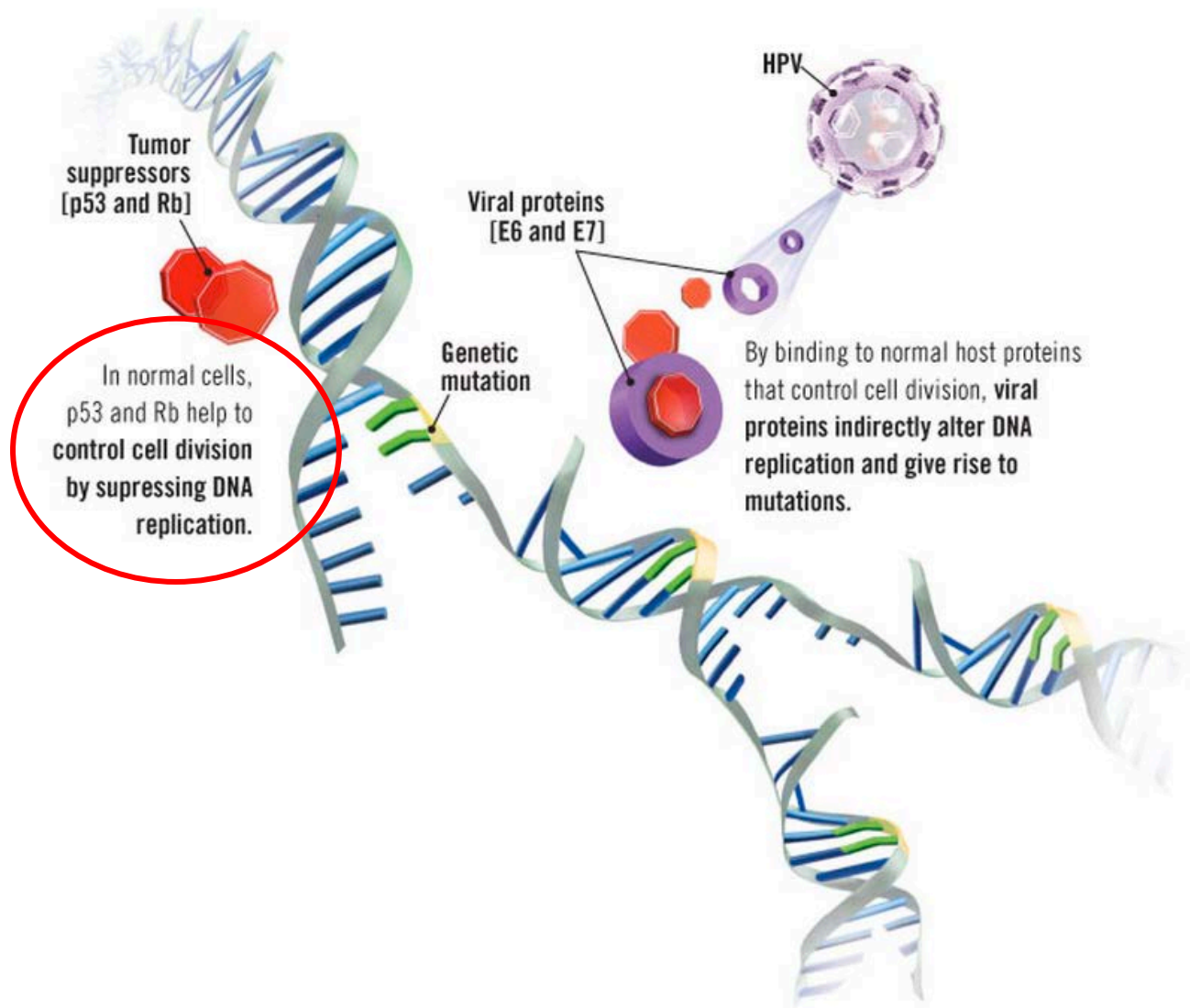
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# HPV E6/E7 –induced oncogenesis

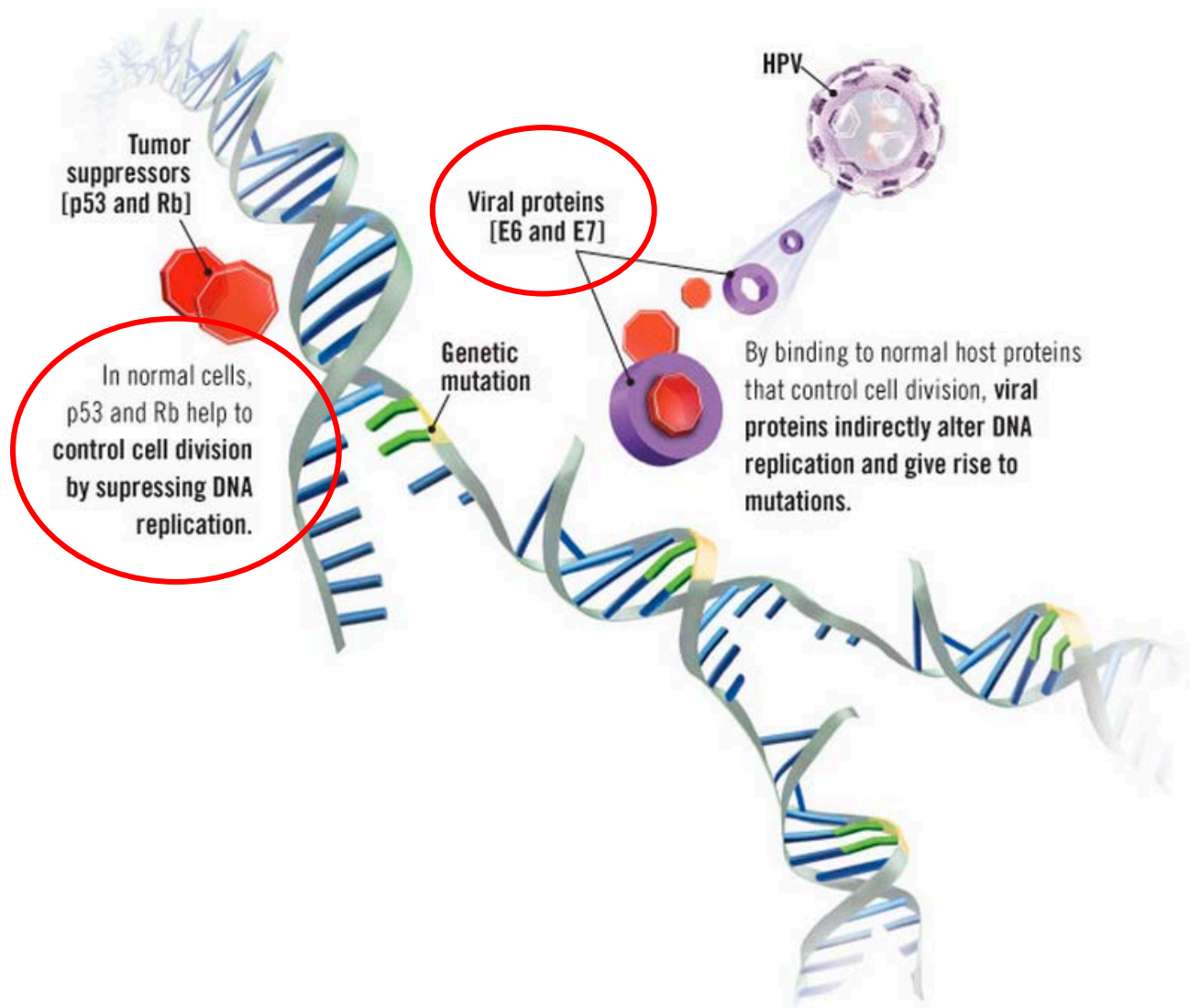




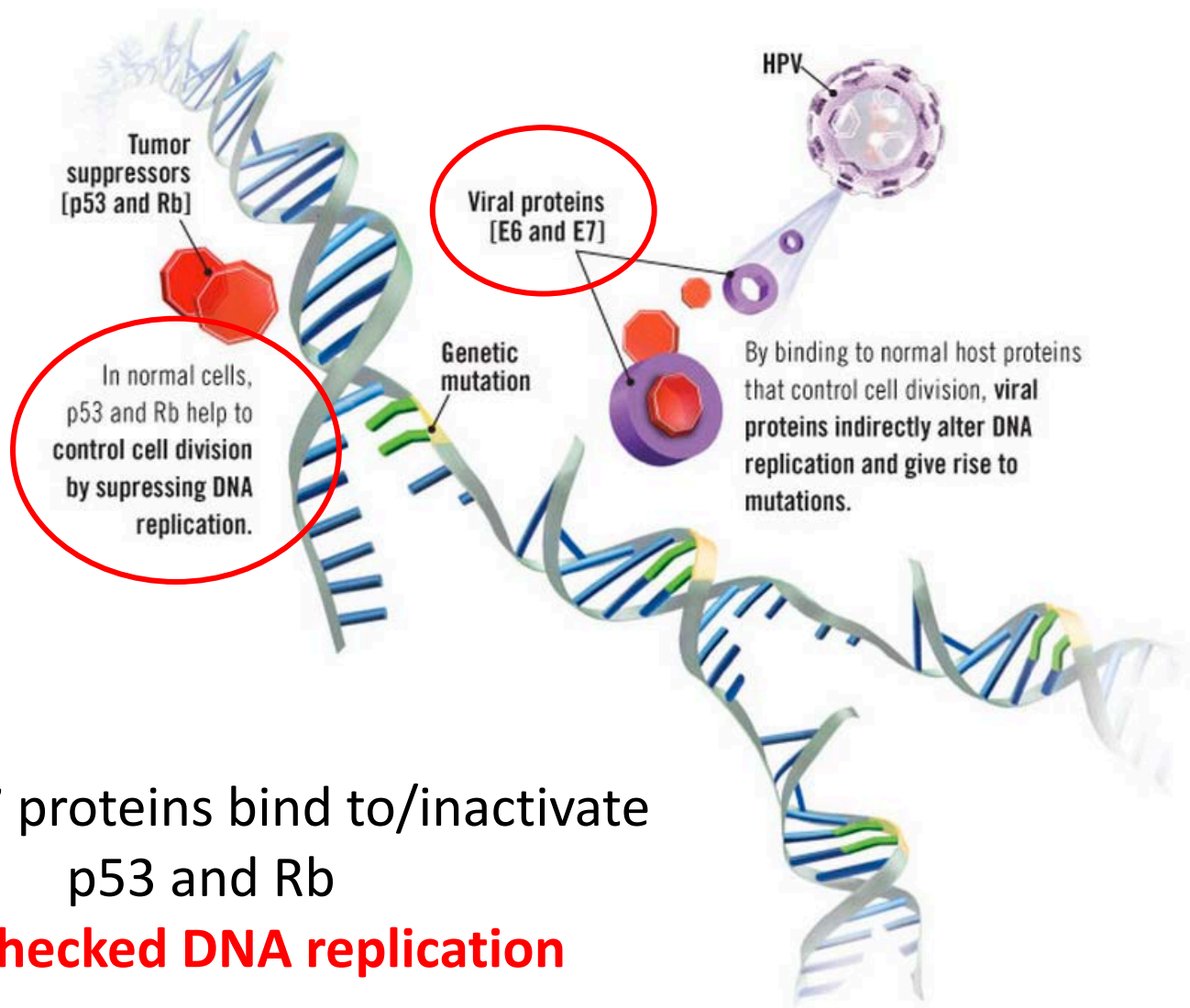
# HPV E6/E7 –induced oncogenesis



# HPV E6/E7 –induced oncogenesis



# HPV E6/E7 –induced oncogenesis



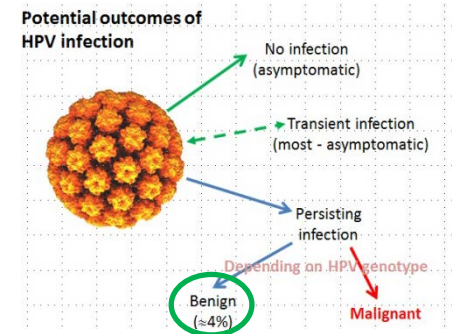
HPV E6/E7 proteins bind to/inactivate  
p53 and Rb

→ **unchecked DNA replication**



### 3 Clinical characteristics – “benign”

- Most infections are asymptomatic
- Highly infectious
- Exposure almost universal
- Commonest STI ( $\approx 4\%$  pop)
- HPV types 6/11 gain entry at sites of epithelial trauma
- Disfiguring
- Psychological & relationship consequences

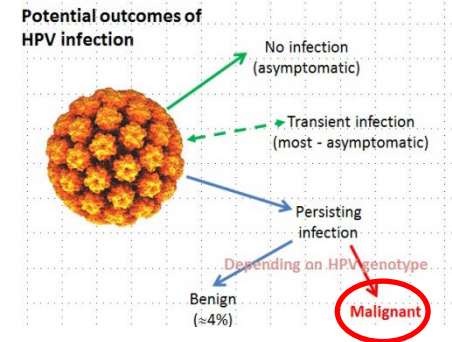


### 3 Benign HPV treatment

- No treatments directly eliminate HPV
- Seek to expose immune system to HPV antigens & enhance response
  - cryotherapy, cautery (surgery)
  - podophyllotoxin, imiquimod
- Work in  $\approx 75\%$  of cases
- $\approx 25\%$  recurrences
- 10% will have another STI

### 3 Clinical characteristics - malignant

- Best understood for cervix
- Initial stages are asymptomatic
- HPV16 = commonest type
- Exposure almost universal
- Infectious
- Causes  $\approx 5\%$  of global cancers
- HPV gain entry at sites of epithelial trauma
- Prognosis closely related to stage at diagnosis
- $\approx 65\%$  five year survival



# **Malignant HPV Infection**

### 3 Clinical characteristics - treatment

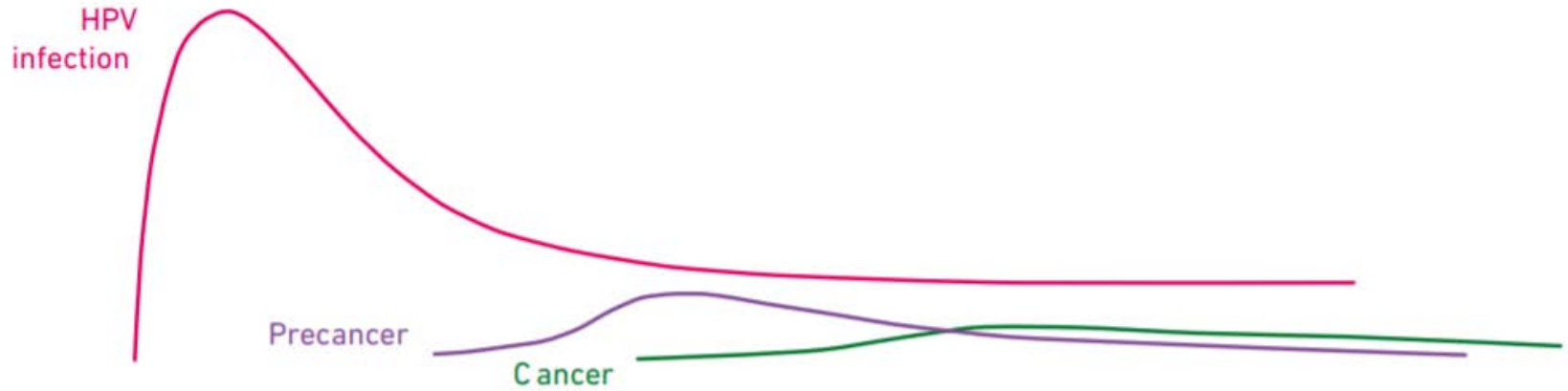
- Prognosis closely related to stage at diagnosis
- HSIL (“CIN2/3”) treatment best established for cervix
- Rx varies with site:
  - loop excision
  - surgery – often extensive
  - chemoradiotherapy
  - PD1 blockers promising
- $\approx$  65% five year survival (unless screening in place)

**3**

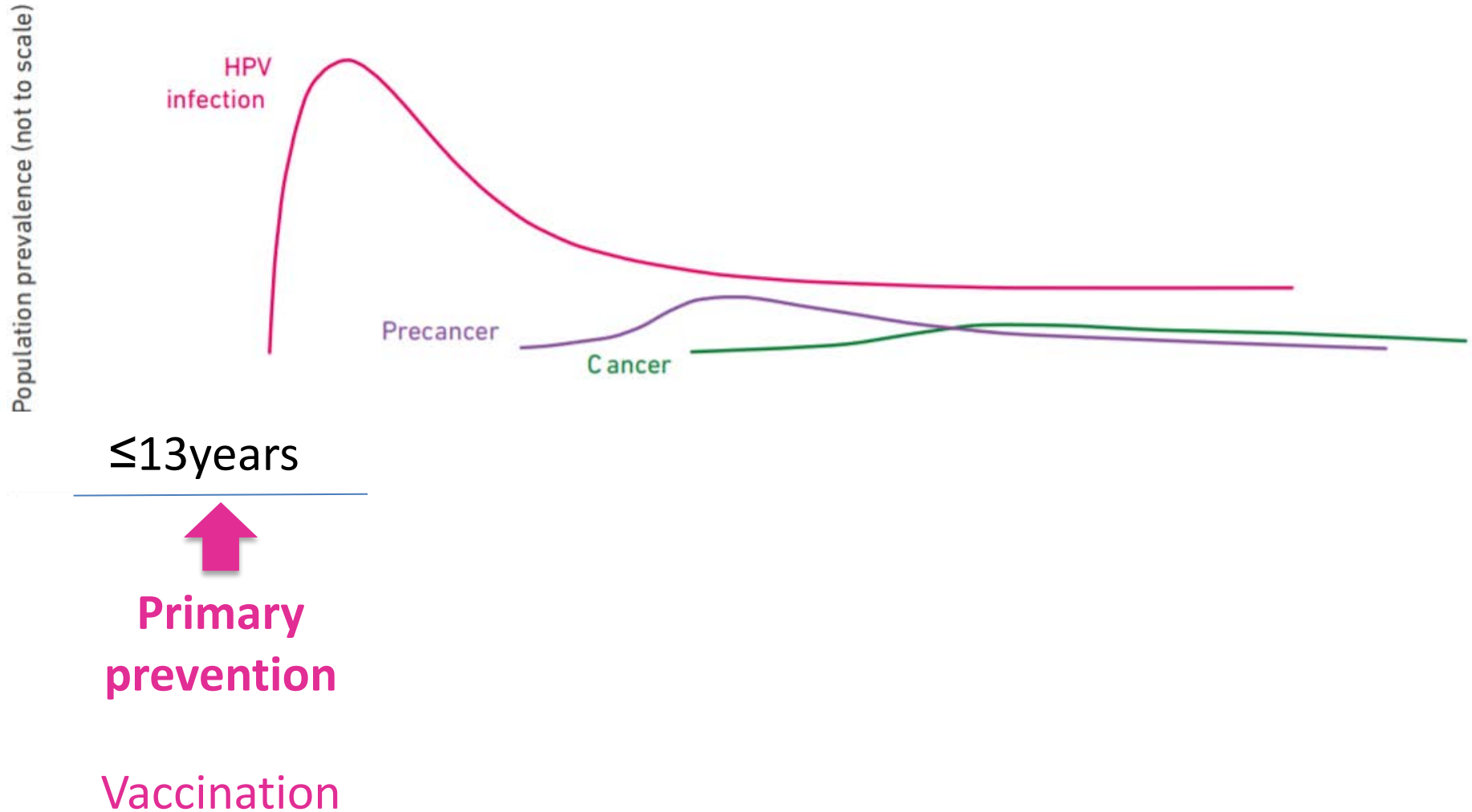
# **Prevention**

# Preventing HPV-related diseases

Population prevalence (not to scale)

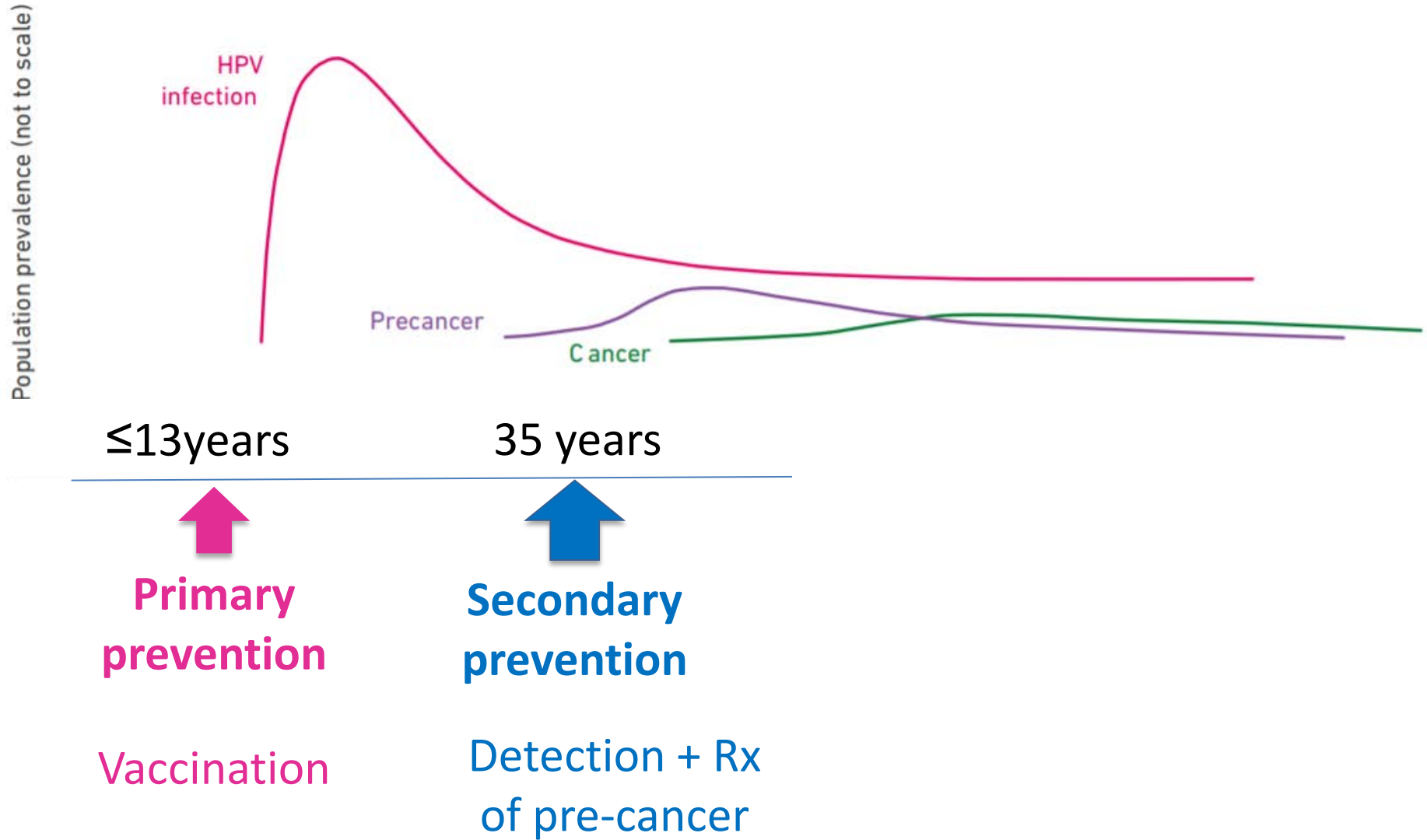


# Preventing HPV-related diseases

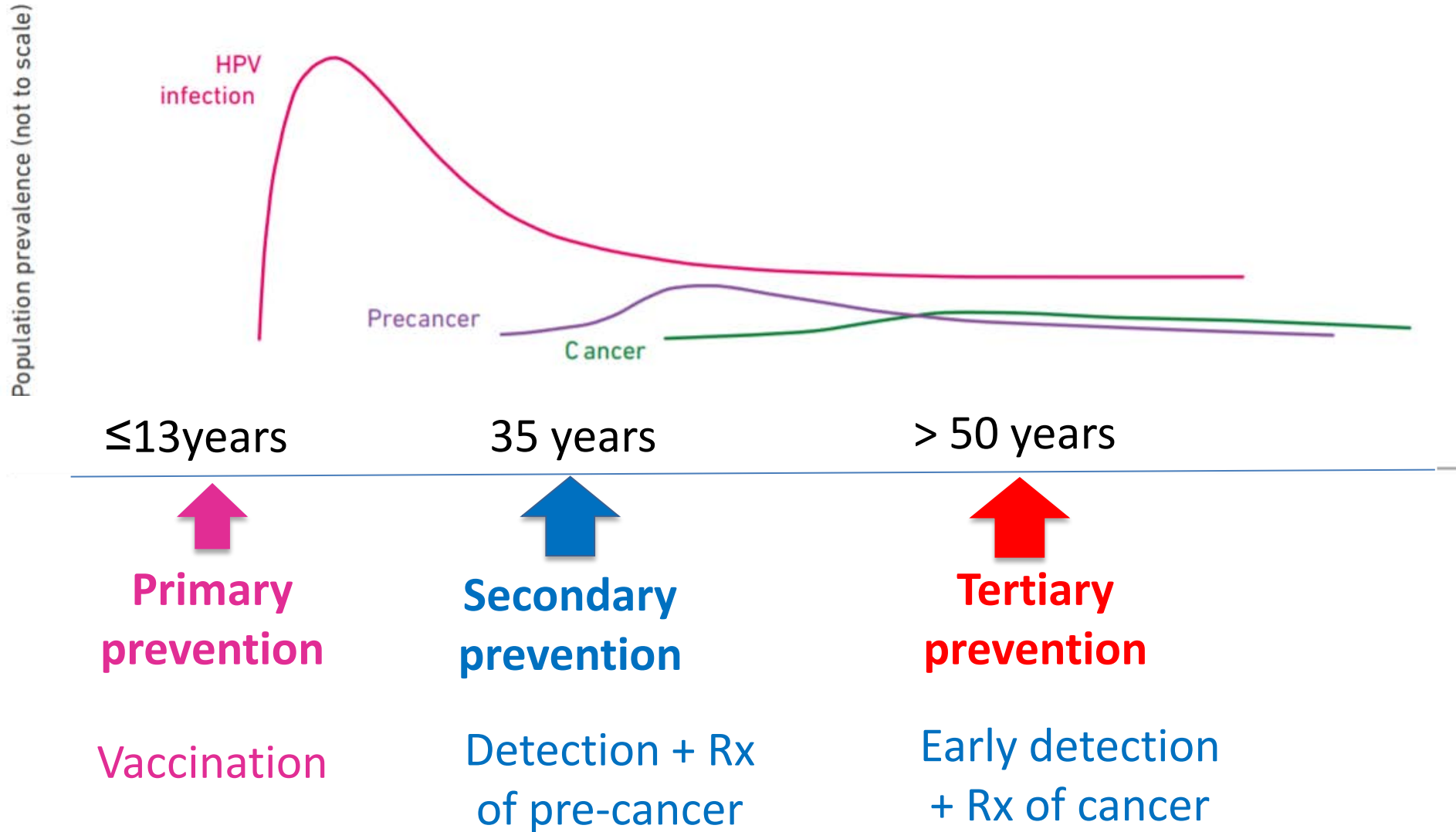




# Preventing HPV-related diseases

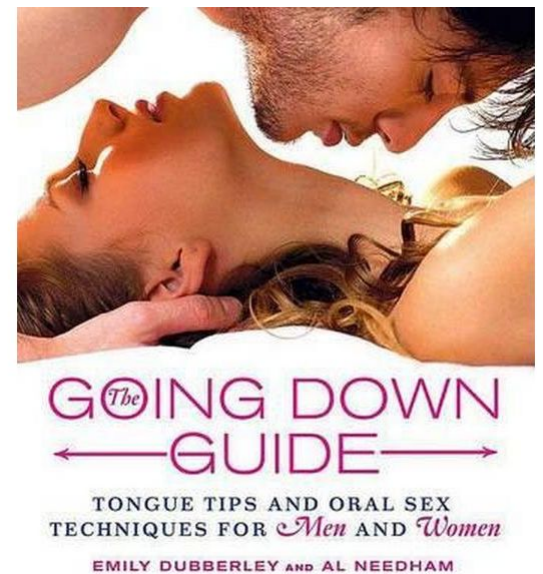


# Preventing HPV-related diseases



**3**

# **1° Prevention**



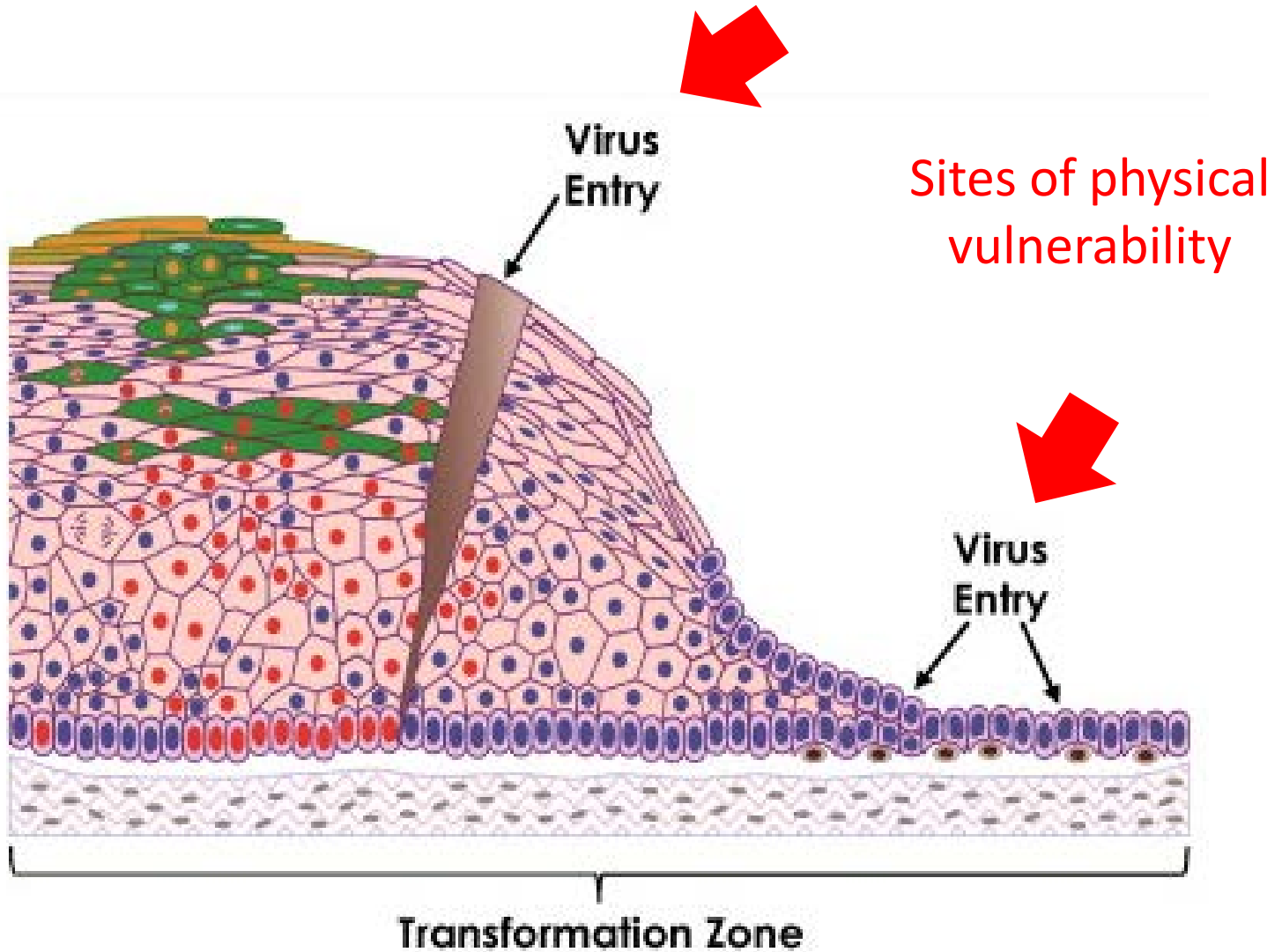
- HPV highly infectious
- Oral & digital transmission
- Does not require penetrative sex
- Condoms only partially protective (25-60%)



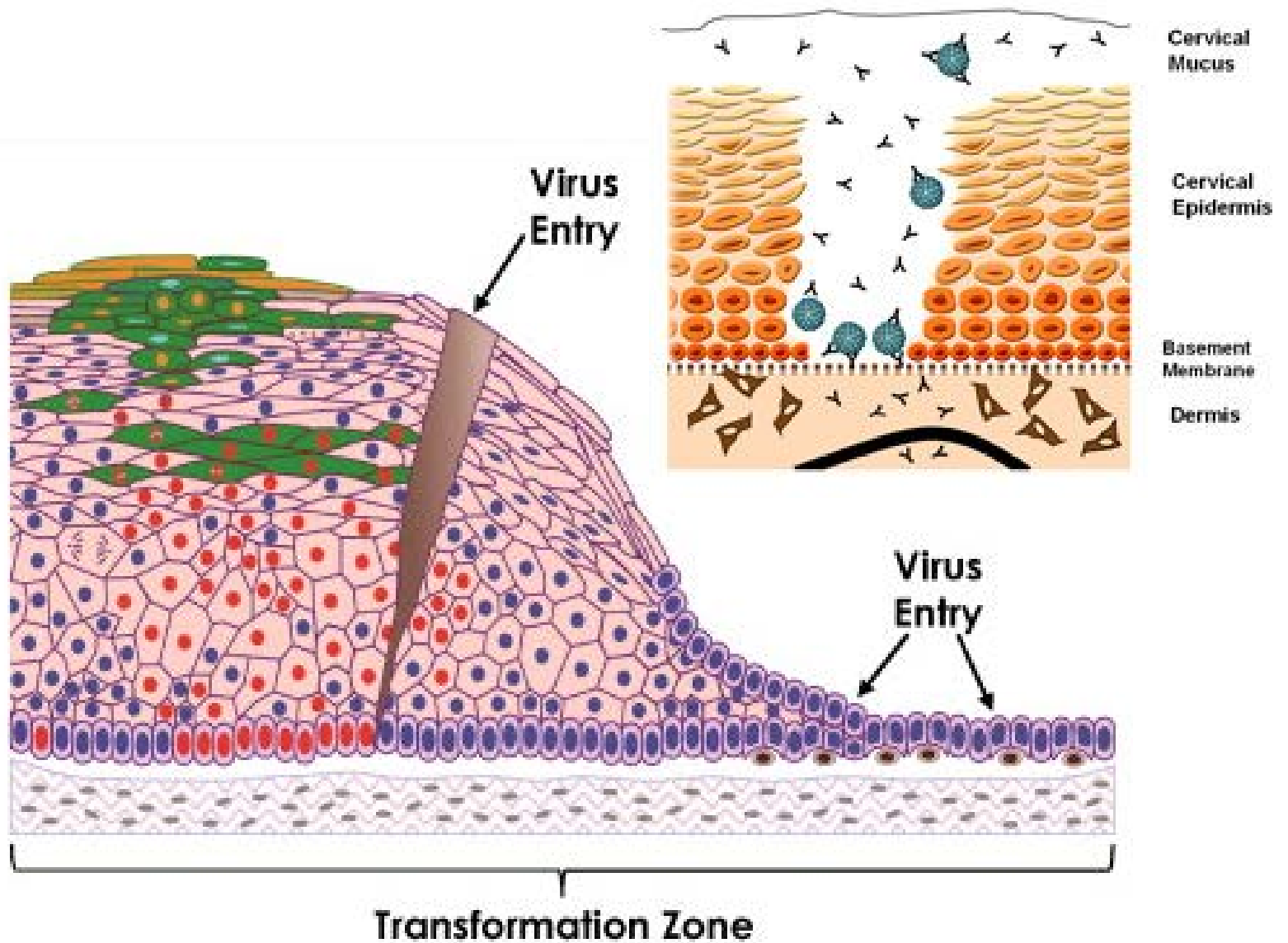
# Prophylactic vaccination

- Highly immunogenic (VLP)
- Local toxicity ( $\approx$  85% soreness)
- No convincing evidence of systemic toxicity from double blind trials (>100,000 recipients)
- Potential to save millions of young lives
- Must be given prior to exposure
- 100% efficacy to >14 years
- Some evidence of cross-protection to closely related HPV genotypes
- Not a therapeutic vaccine

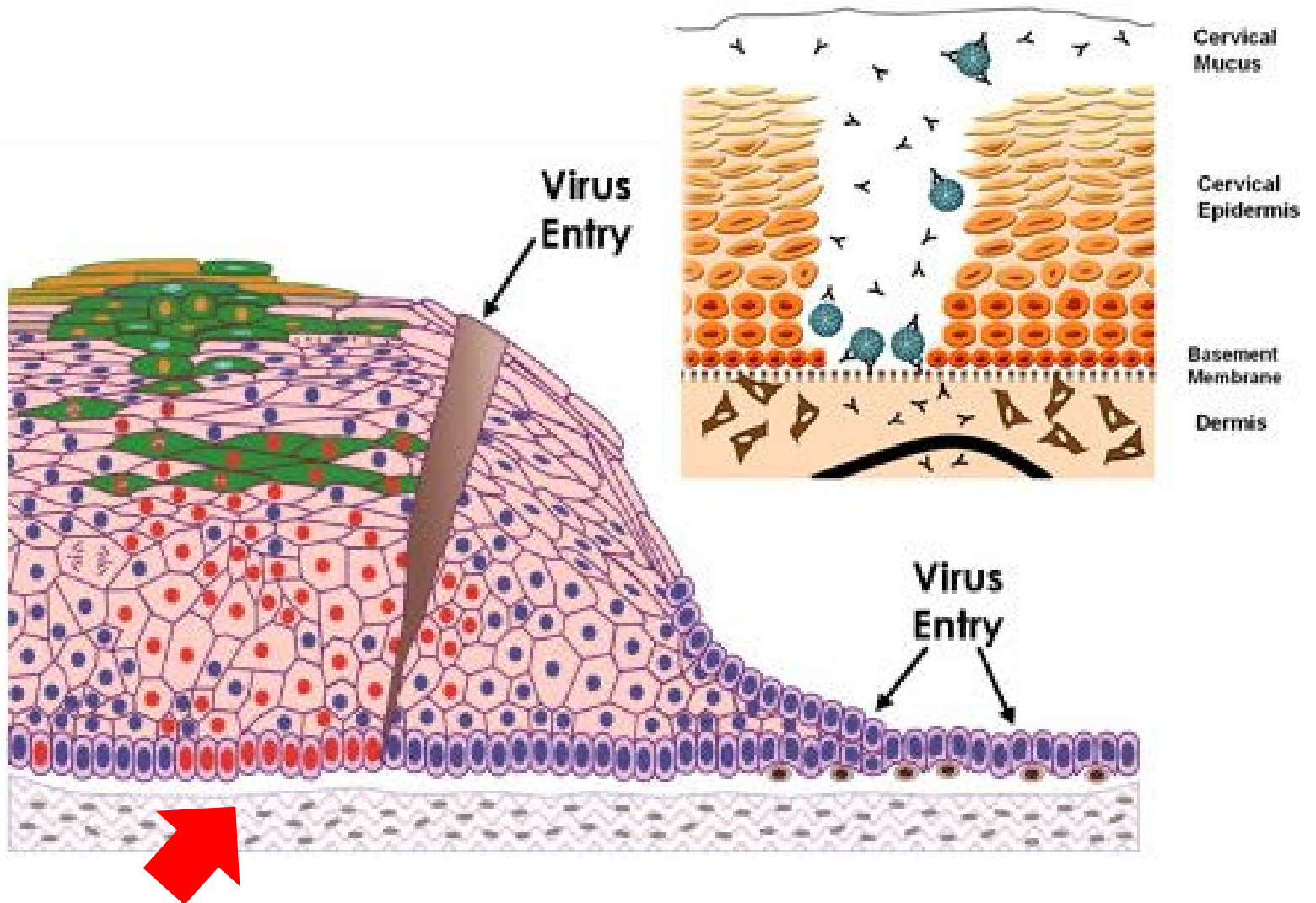
# Prophylactic HPV vaccination



# Prophylactic HPV vaccination



# Prophylactic HPV vaccination



No effect on cells already infected with HPV



# 3

## Australian experience

### Female vaccination

**Since 2006:**

12-13 years + catch up for < 24yrs

### Male vaccination

**Since 2013:**

12-13 years + 2014 catch up for 14-15 yrs



# 3

## Australian experience

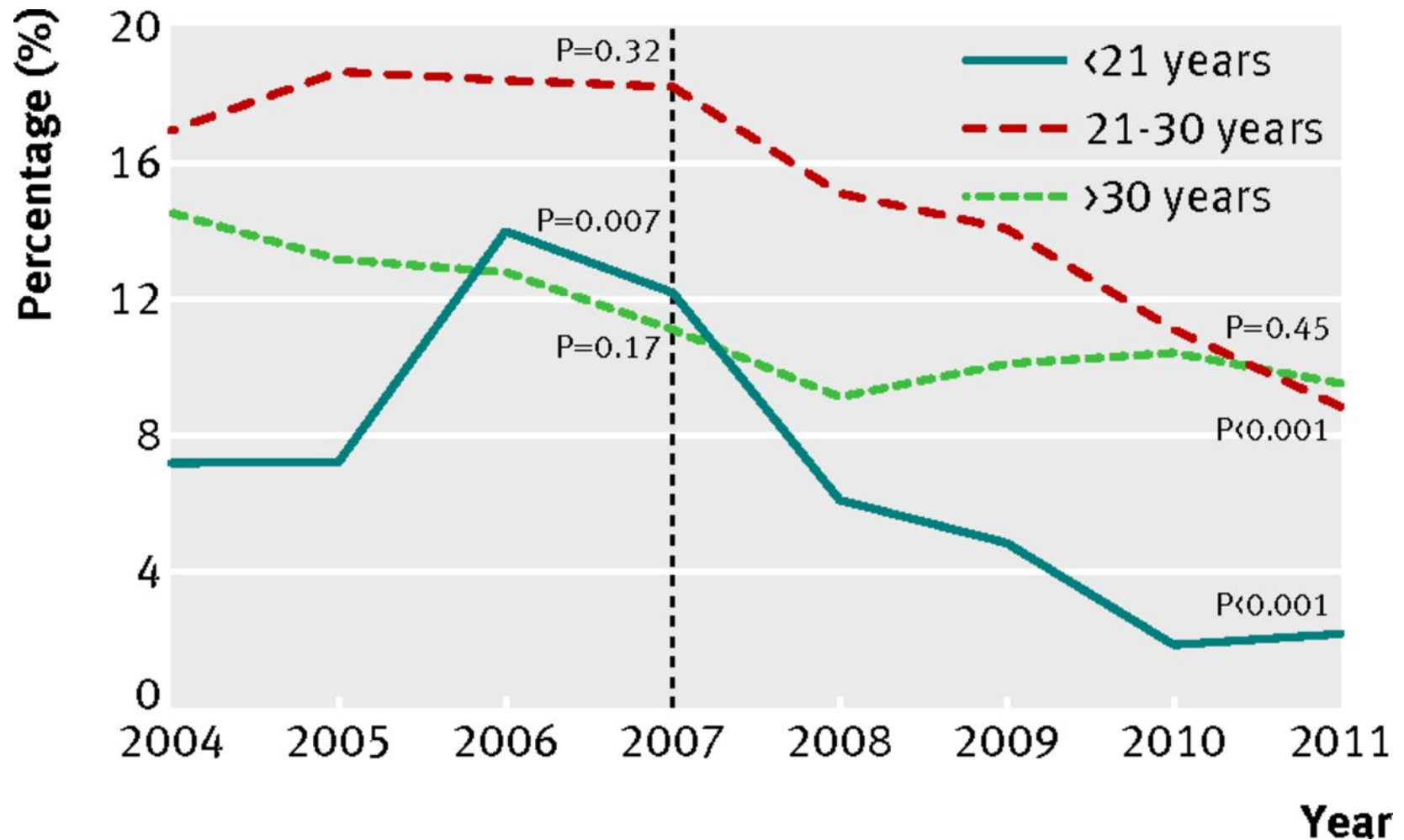
≈ 75% uptake of vaccine

### From 2018:

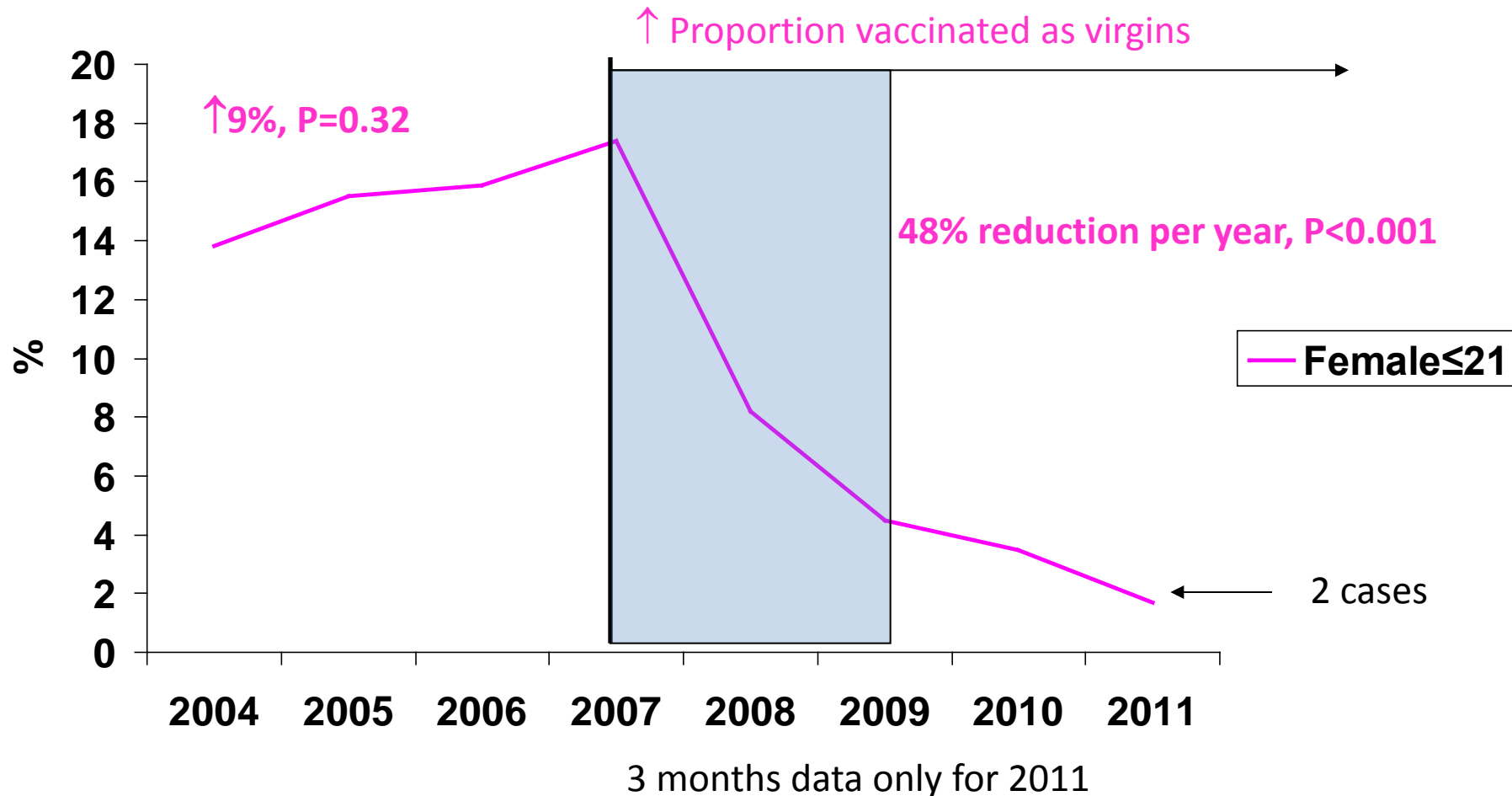
- Switched to x 2 doses of Gardasil 9
- HPV-based cervical screening



# % Australian born het ♀ genital warts at 1st visit

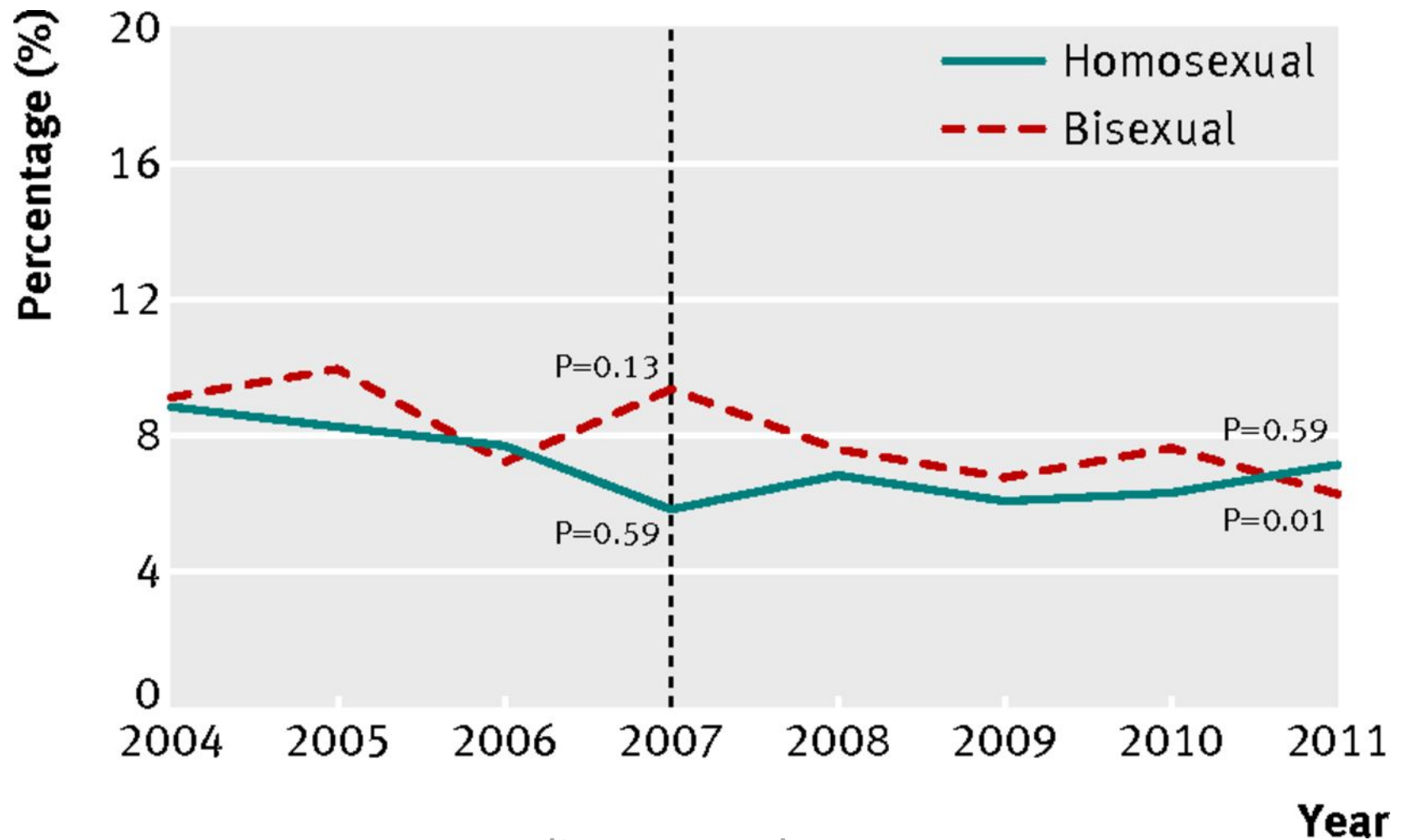


# Female patients by age of $\leq 21$ at consultation (only eligible women $<28$ in 2007)



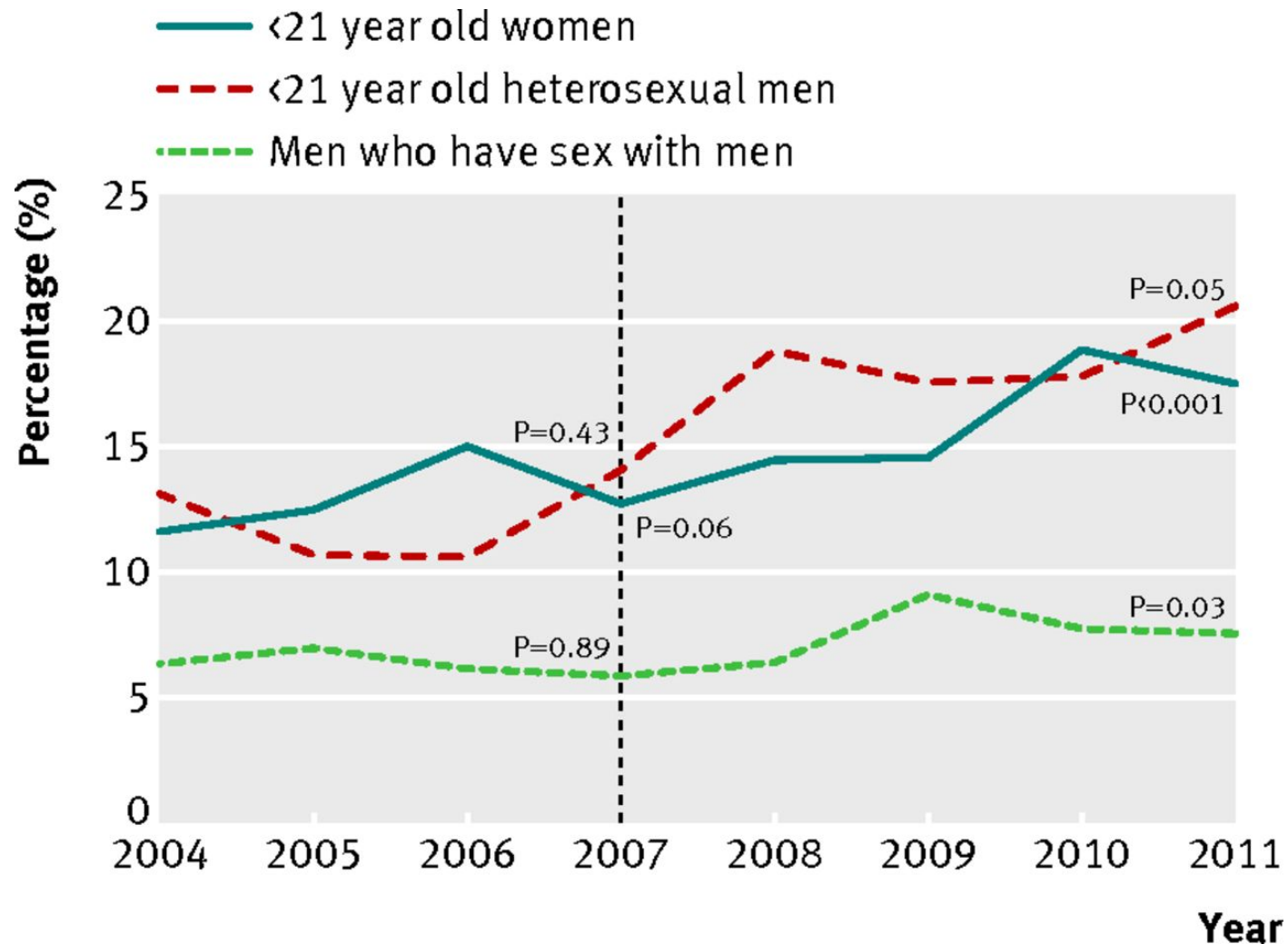
Median age vaginal sex in women Australia about 16-17  
Assume by 2011 many women  $\leq 21$  will have not had sex and  
Will have received the HPV vaccine at School

## % Australian born MSM with genital warts at 1st visit



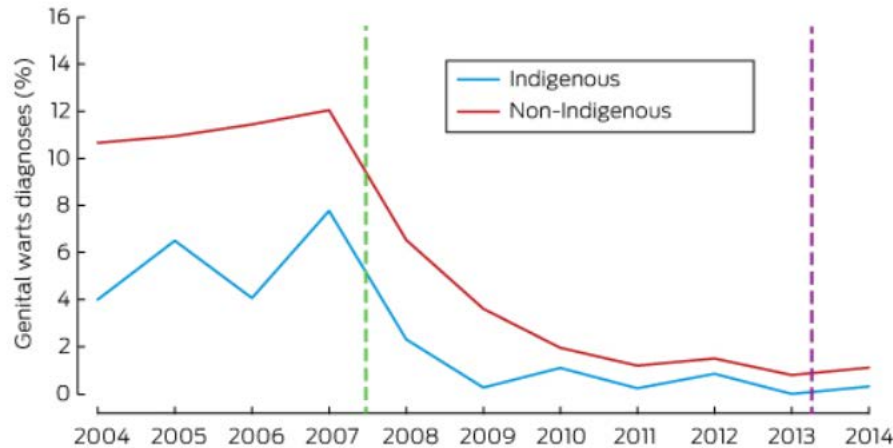
Ali H Br Med J 2013;346:2032

# Australian born with chlamydia at 1st visit



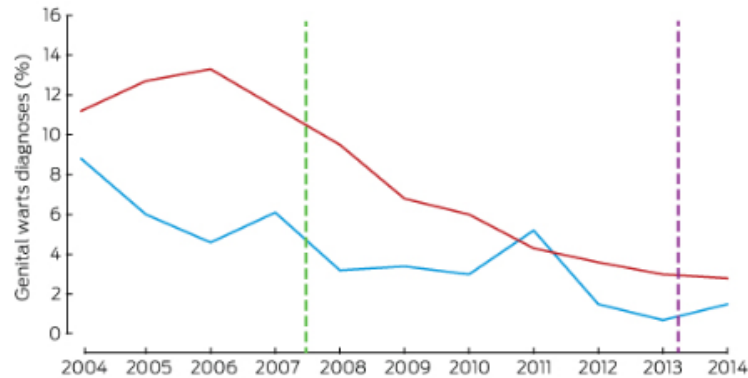
< > **Box 1 – Proportion of Indigenous and non-Indigenous Australian-born women diagnosed with genital warts at first visit to a sexual health clinic, 2004–2014\***

**A. Under 21 years of age**

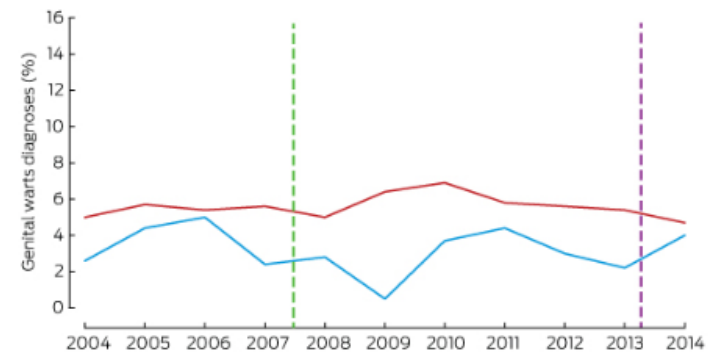


Sylvan Grandadam / robertharding via Getty Images

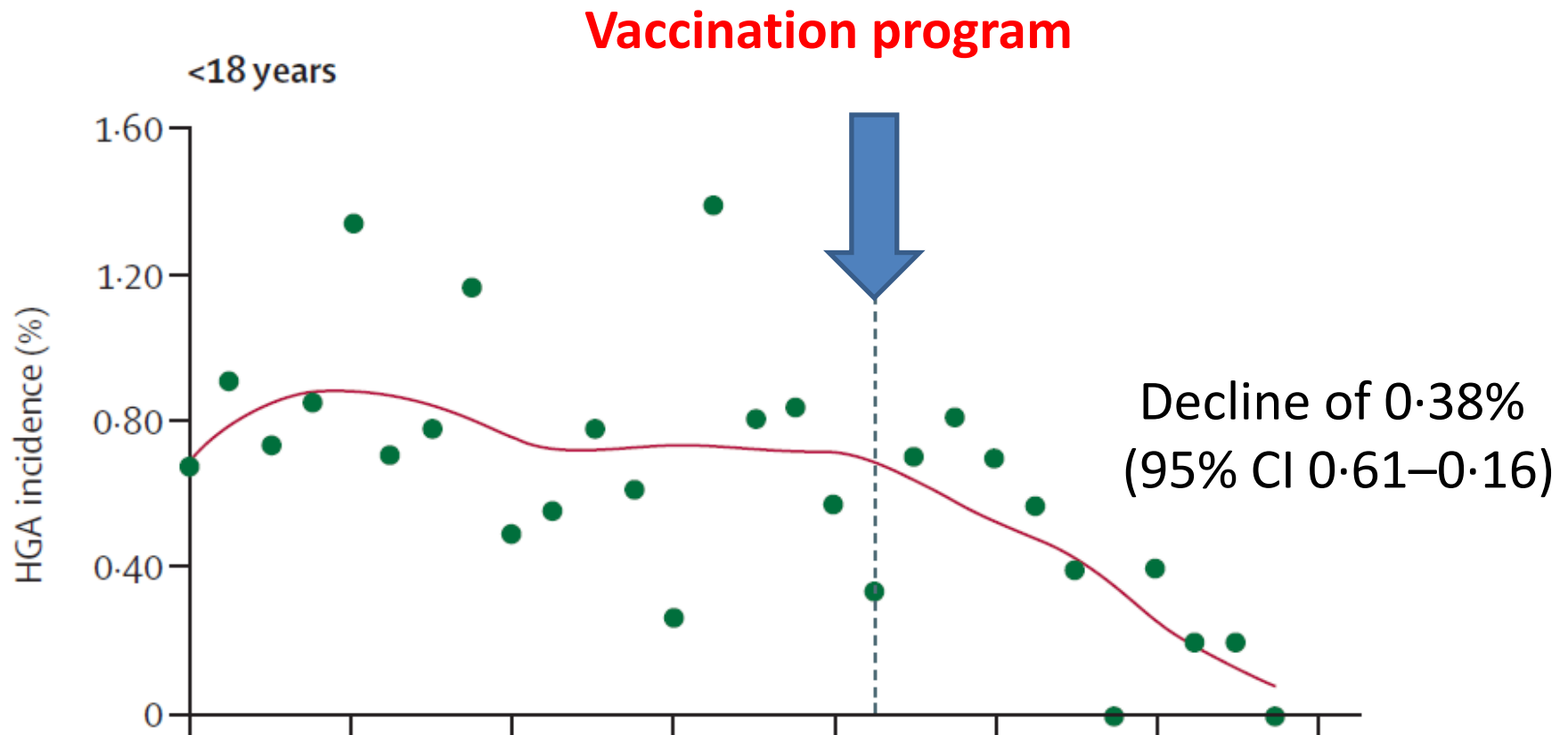
**B. 21–30 years of age**



**C. Over 30 years of age**



# Incidence of high-grade cervical abnormalities



No effect in  
older groups



# HPV vaccination coverage in different countries

Country	Target age group	Coverage (3 doses)	Delivery method
Luxembourg	12	17% (2009)	Health care providers (free of charge)
France	14	24% (2008)	Health care providers (co payment basis)
Norway	12	30% (2010)	School based
US	13-17	32% (2010)	Health care providers
Netherlands	12	45% (2009)	Health care providers (free of charge)
Italy	11	56% (2009)	Health care providers (free of charge)
Denmark	12	58% (2010)	Health care providers (free of charge)
Australia	12	64-80% (2009)	School based (free of charge)
UK	12	80% (2009)	School based (free of charge)
Portugal	13	81% (2009)	School based (free of charge)

# Population-based meta-analysis

**140 million person-years** of follow-up data

Nine high-income countries with high vaccination coverage:

- ↓HPV16 + HPV18 infection + AGW by > 60% in girls <20 years of age
- Significant evidence of vaccine cross-protection and herd effects:
  - ↓ in HPV31, HPV33, and HPV45 in girls <20 years
  - ↓ AGW in men and older women

# Population-based meta-analysis

## Countries with low vaccination coverage:

- Significant ↓ in HPV16 + HPV18 + AGW in girls <20 years of age
- No change in:
  - HPV31, HPV33, and HPV45 infections
  - HPV-related outcomes in boys, men, and older women

(i.e. no indication of cross-protection or herd effects)

- Optimising vaccine delivery
  - include boys
  - improved access for girls
  - smaller number of doses
  - when/if need to boost
  - extend to older groups?

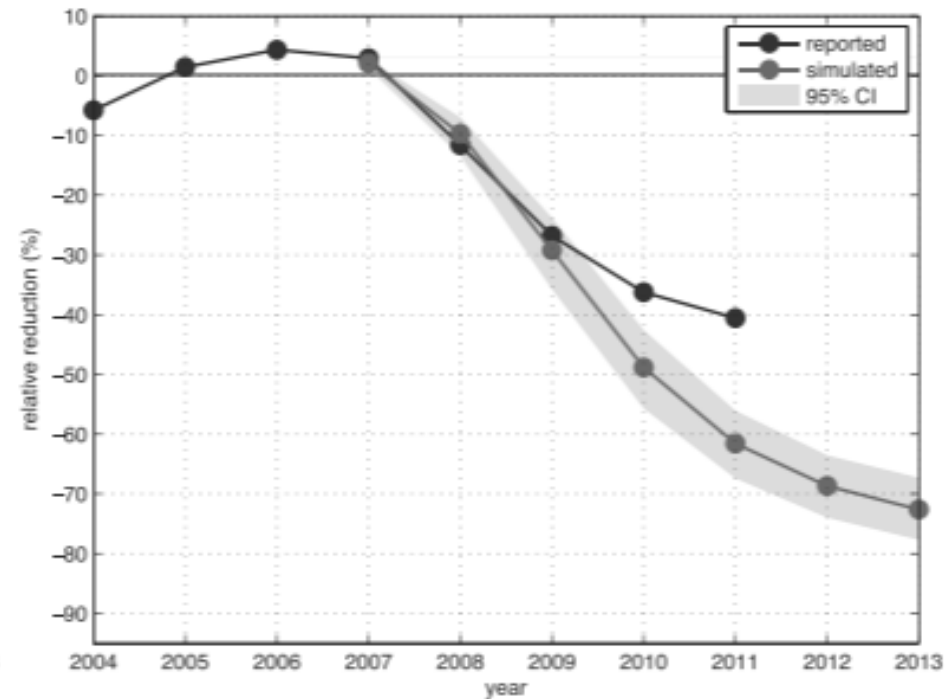
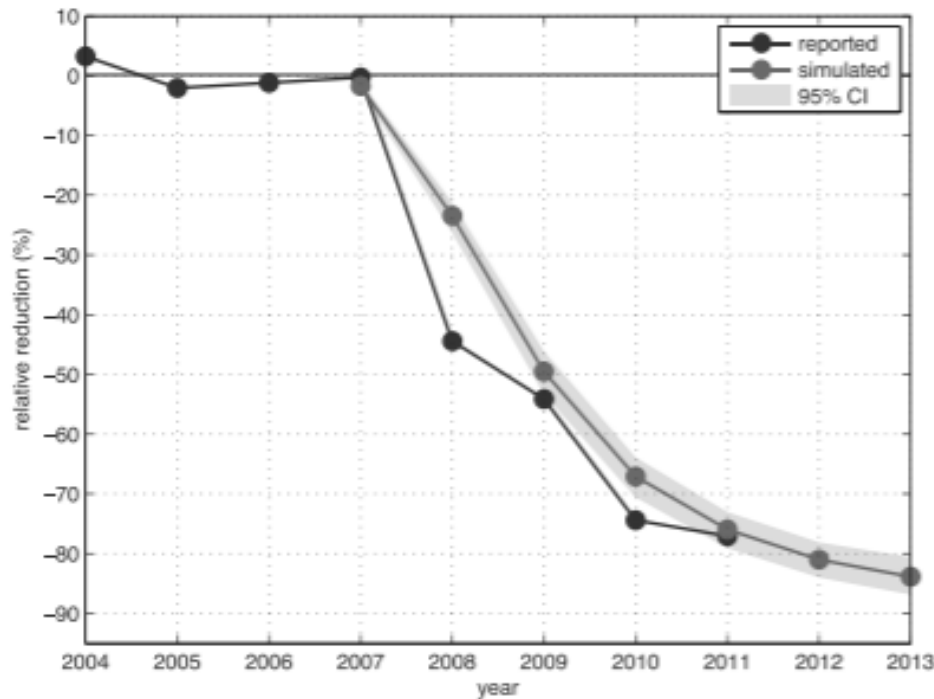
# The argument for gender-neutral vaccination

# Near Elimination of Genital Warts in Australia Predicted With Extension of Human Papillomavirus Vaccination to Males

Female

Current situation

Male



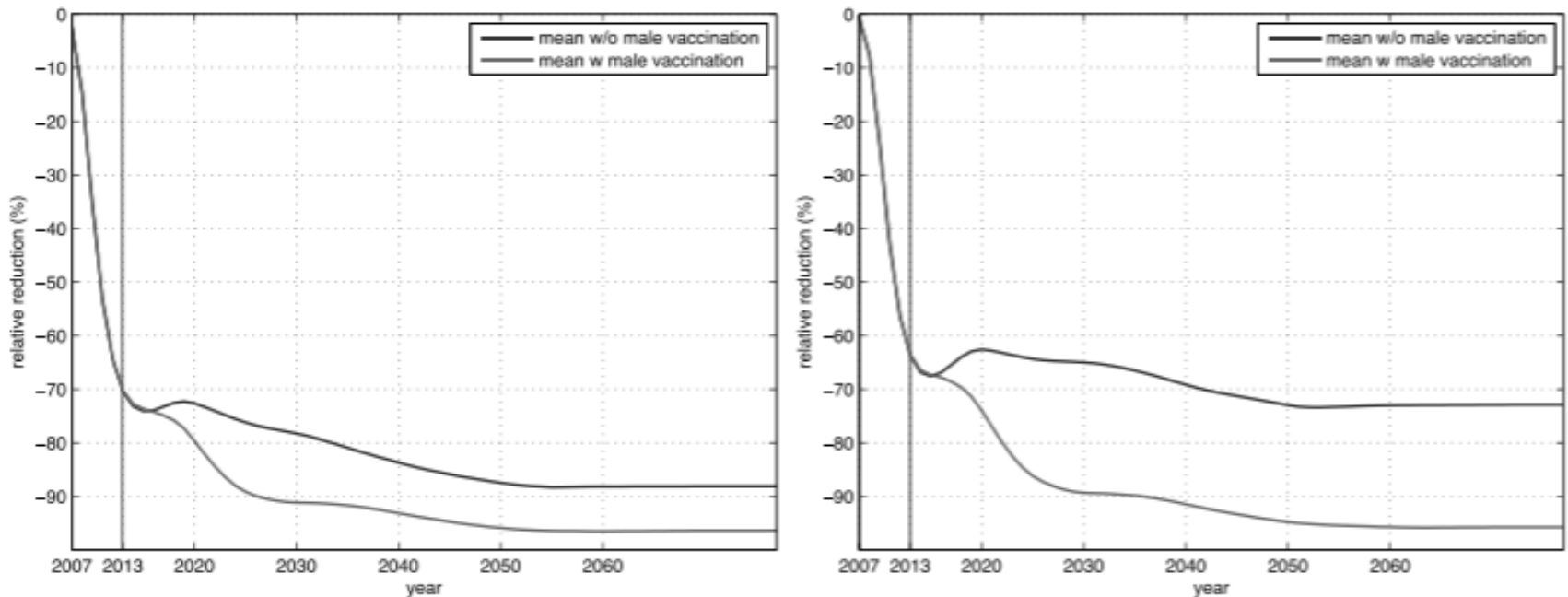
**Figure 2.** Relative reductions in genital wart incidence in Australian resident females (left) and males (right); before 2007, the reductions are shown for those aged 12 to 26 years, whereas from 2007, they are for the cohort who were aged 12 to 26 in 2007 and 16 to 30 in 2011. The solid lines are posterior means, whereas the area between the 97.5% and 2.5% posterior percentiles is marked as the 95% confidence interval.

# Near Elimination of Genital Warts in Australia Predicted With Extension of Human Papillomavirus Vaccination to Males

Female

Future models

Male



**Figure 3.** Predicted reductions in genital wart incidence in the whole Australian sexually active female (left) and male (right) populations under the current NIP and its extension to include male HPV vaccination commencing in 2013. The solid lines are posterior means, whereas the area between the 97.5% and 2.5% posterior percentiles is marked as the 95% confidence interval.

Hindawi  
Journal of Immunology Research  
Volume 2017, Article ID 3736201, 6 pages  
<https://doi.org/10.1155/2017/3736201>

## *Review Article*

# **Safety of Human Papillomavirus 9-Valent Vaccine: A Meta-Analysis of Randomized Trials**

**Ana Paula Ferreira Costa,<sup>1</sup> Ricardo Ney Oliveira Cobucci,<sup>2</sup> Janine Medeiros da Silva,<sup>3</sup> Paulo Henrique da Costa Lima,<sup>3</sup> Paulo César Giraldo,<sup>4</sup> and Ana Katherine Gonçalves<sup>1,3</sup>**

<sup>1</sup>*Postgraduate Program in Health Sciences, Federal University of Rio Grande do Norte, Natal, RN, Brazil*



# Challenges to HPV vax programs

- Silent epidemic
- Female empowerment
- Fake news
- Maintaining momentum
- Surveillance to demonstrate efficacy



**Vaccine Creator  
Dr. Diane Harper  
Confesses:  
Gardasil Is More  
Dangerous Than  
The HPV virus  
it was made  
to prevent!**



# Summary

- ✓ Understand the importance of HPV in human disease
- ✓ Outline the basic virology and pathogenesis of HPV-related conditions
- ✓ Describe the clinical characteristics and epidemiologies of the major HPV-related diseases
- ✓ Evaluate current international progress towards the elimination of HPV
- ✓ Discuss challenges to the implementation of elimination programs

唔該曬



## High Resolution Anoscopy Workshop 2018

29-30 September 2018 \*

St Vincent's Hospital, Sydney, Australia  
[www.iansoc.org](http://www.iansoc.org)

\* This will take place alongside HPV 2018 – The 32nd International Papillomavirus Conference (1-6 October 2018)

**ipvc 2018**

**32<sup>ND</sup> INTERNATIONAL  
PAPILLOMAVIRUS CONFERENCE (HPV)**

OCTOBER 2-6, 2018 | SYDNEY, AUSTRALIA

Basic Science to Global Health Impact

 **International  
Papillomavirus Society**

[www.ipvc2018.org](http://www.ipvc2018.org)

**TAKE A CHANCE  
ON LOVE.  
NOT HPV.**

