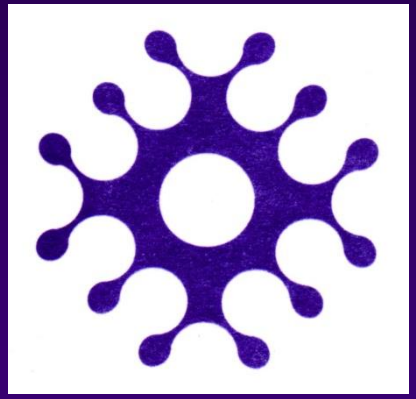
Pathogenesis and diagnosis of clinically relevant HPV infections

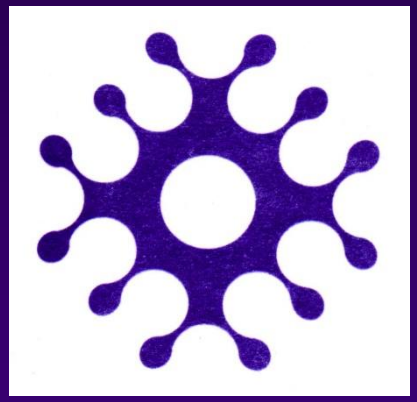


Mario Poljak

Institute of Microbiology and Immunology
Faculty of Medicine, University of Ljubljana, Slovenia

HPV İMMÜN YANITI:

ENFEKSİYON MEKANİZMASI VE KORUNMA



Mario Poljak

Mikrobiyoloji ve İmmünoloji Enstitüsü
Ljubljana Tıp Fakültesi, Slovenya

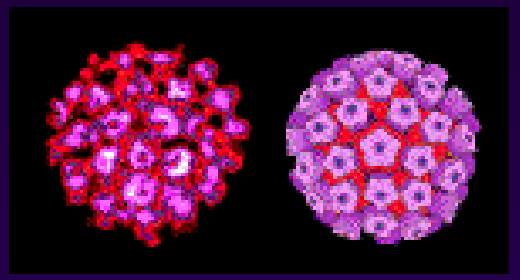

ESCMID
EUROPEAN SOCIETY
OF CLINICAL MICROBIOLOGY
AND INFECTIOUS DISEASES
14th ESCMID
Summer School
Istanbul, Turkey
4 – 11 July, 2015


CEPHANECİOĞLU
İŞTAH TURŞULARI

Classification of HPVs

HPV

Viral characteristics



- non-enveloped viruses; icosahedral capsid

- remarkably diverse BUT remarkably genetically stable
  (diverged since the origin of humanity only by about 2%)

- classified by the homology of their genome into many genotypes

- genotypes numbered chronologically in order of characterization

International HPV Reference Center
http://www.nordicehealth.se/hpvcenter/reference_clones/
The PapillomaVirus Episteme (PaVE)
http://pave.niaid.nih.gov/#home
status: 12. 03. 2019

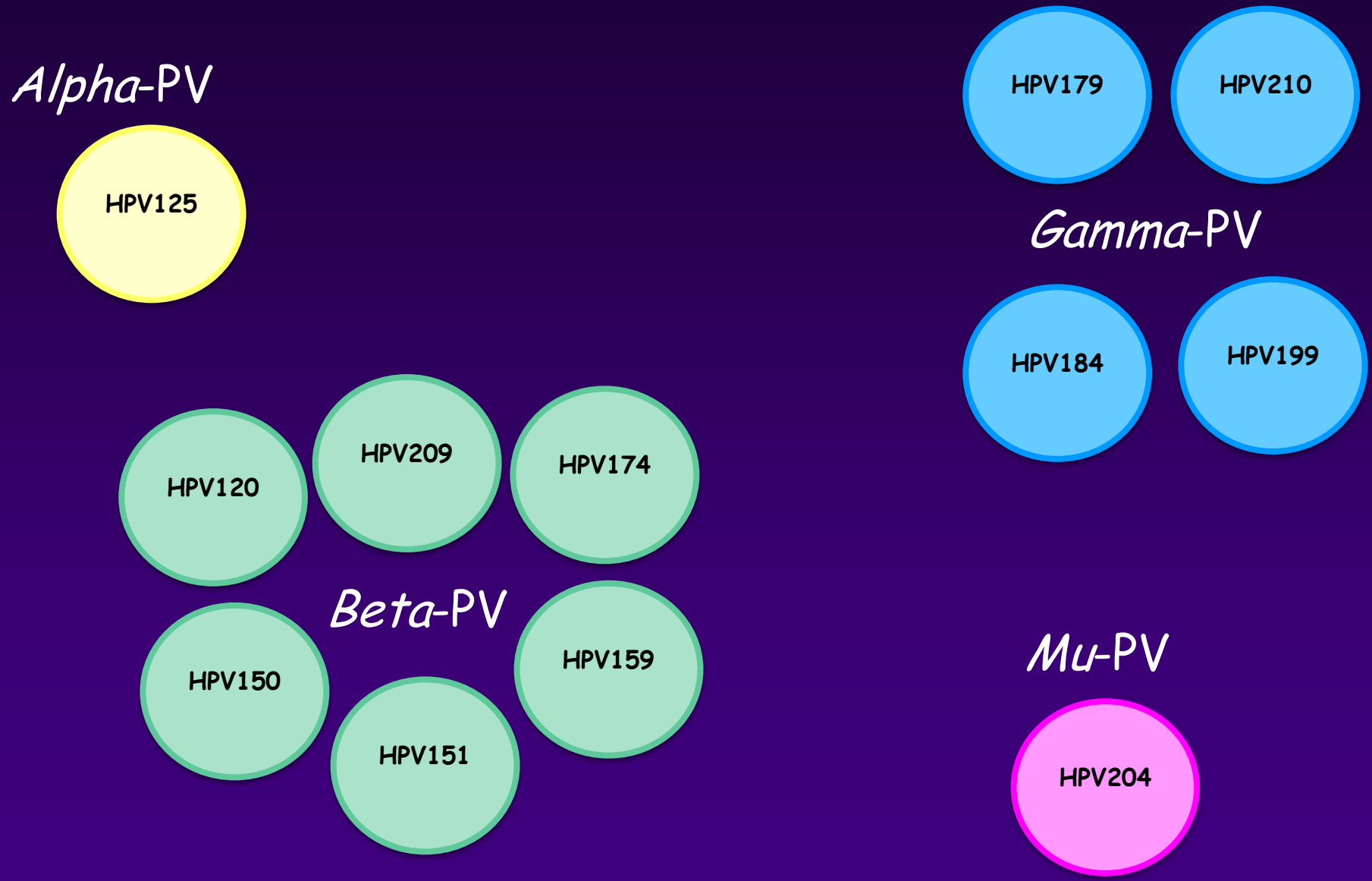
HPV-226

222 official HPV genotypes

HPV-46, HPV-55, HPV-64 and HPV-79 did not meet the criteria as a unique HPV


HPV 717

HPV types characterized in Slovenia



RESEARCH ARTICLE

PLoS ONE 2017;12:e0175892

Molecular characterization, tissue tropism, and genetic variability of the novel *Mupapillomavirus* type HPV204 and phylogenetically related types HPV1 and HPV63

Anja Šterbenc[1], Lea Hošnjak[1], Diego Chouhy[2], Elisa M. Bolatti[2], Anja Oštrbenk[1], Katja Seme[1], Boštjan J. Kocjan[1], Boštjan Luzar[3], Adriana A. Giri[2], Mario Poljak[1]*

1 Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, **2** Virology Area, School of Biochemistry and Pharmaceutical Sciences, Rosario National University, Rosario, Argentina, **3** Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Global Genomic Diversity of Human Papillomavirus 6 Based on 724 Isolates and 190 Complete Genome Sequences

J Virol 2014;88:7307-16.

Mateja M. Jelen,[a] Zigui Chen,[b] Boštjan J. Kocjan,[a] Felicity J. Burt,[c] Paul K. S. Chan,[d] Diego Chouhy,[e] Catharina E. Combrinck,[c] François Coutlée,[f] Christine Estrade,[g] Alex Ferenczy,[h] Alison Fiander,[i] Eduardo L. Franco,[j] Suzanne M. Garland,[k,l,m] Adriana A. Giri,[e] Joaquín Víctor González,[n] Arndt Gröning,[o] Kerstin Heidrich,[o] Sam Hibbitts,[i] Lea Hošnjak,[a] Tommy N. M. Luk,[p,q] Karina Marinic,[r] Toshihiko Matsukura,[s] Anna Neumann,[o] Anja Oštrbenk,[a] Maria Alejandra Picconi,[n] Harriet Richardson,[t] Martin Sagadin,[a] Roland Sahli,[g] Riaz Y. Seedat,[u] Katja Seme,[a] Alberto Severini,[v] Jessica L. Sinchi,[r] Jana Smahelova,[w] Sepehr N. Tabrizi,[k,l,m] Ruth Tachezy,[w] Sarah Tohme,[v] Virgilijus Uloza,[x] Astra Vitkauskiene,[y] Yong Wee Wong,[z] Snježana Židovec Lepej,[aa] Robert D. Burk,[ab,b] Mario Poljak[a]

Global Genomic Diversity of Human Papillomavirus 11 Based on 433 Isolates and 78 Complete Genome Sequences

J Virol 2016;90:5503-13.

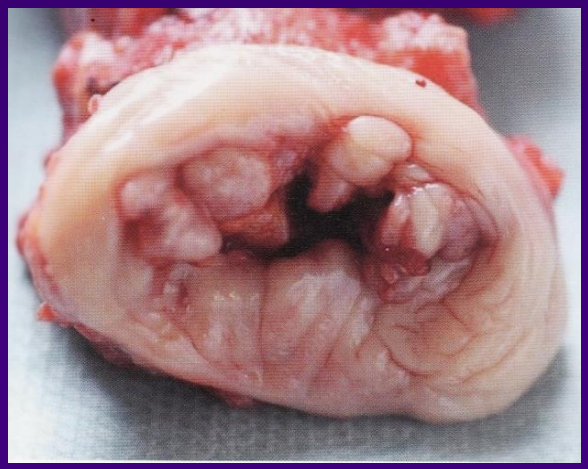
Mateja M. Jelen,[a] Zigui Chen,[b] Boštjan J. Kocjan,[c] Lea Hošnjak,[c] Felicity J. Burt,[d] Paul K. S. Chan,[b] Diego Chouhy,[e] Catharina E. Combrinck,[d] Christine Estrade,[f] Alison Fiander,[g] Suzanne M. Garland,[h,i,j] Adriana A. Giri,[e] Joaquín Víctor González,[k] Arndt Gröning,[l] Sam Hibbitts,[g] Tommy N. M. Luk,[m,n] Karina Marinic,[o] Toshihiko Matsukura,[p] Anna Neumann,[l] Anja Oštrbenk,[c] Maria Alejandra Picconi,[k] Martin Sagadin,[c] Roland Sahli,[f] Riaz Y. Seedat,[q] Katja Seme,[c] Alberto Severini,[r] Jessica L. Sinchi,[o] Jana Smahelova,[s] Sepehr N. Tabrizi,[h,i,j] Ruth Tachezy,[s] Sarah Tohme Faybush,[r] Virgilijus Uloza,[t] Ingrida Uloziene,[t] Yong Wee Wong,[u] Snježana Židovec Lepej,[v] Robert D. Burk,[w] Mario Poljak[c]

- the largest database of globally circulating HPV-6 and HPV-11 genomic variants
- total of 130 new complete HPV-6 genome sequences (out of 190)
- total of 30 new complete HPV-11 genome sequences (out of 78)



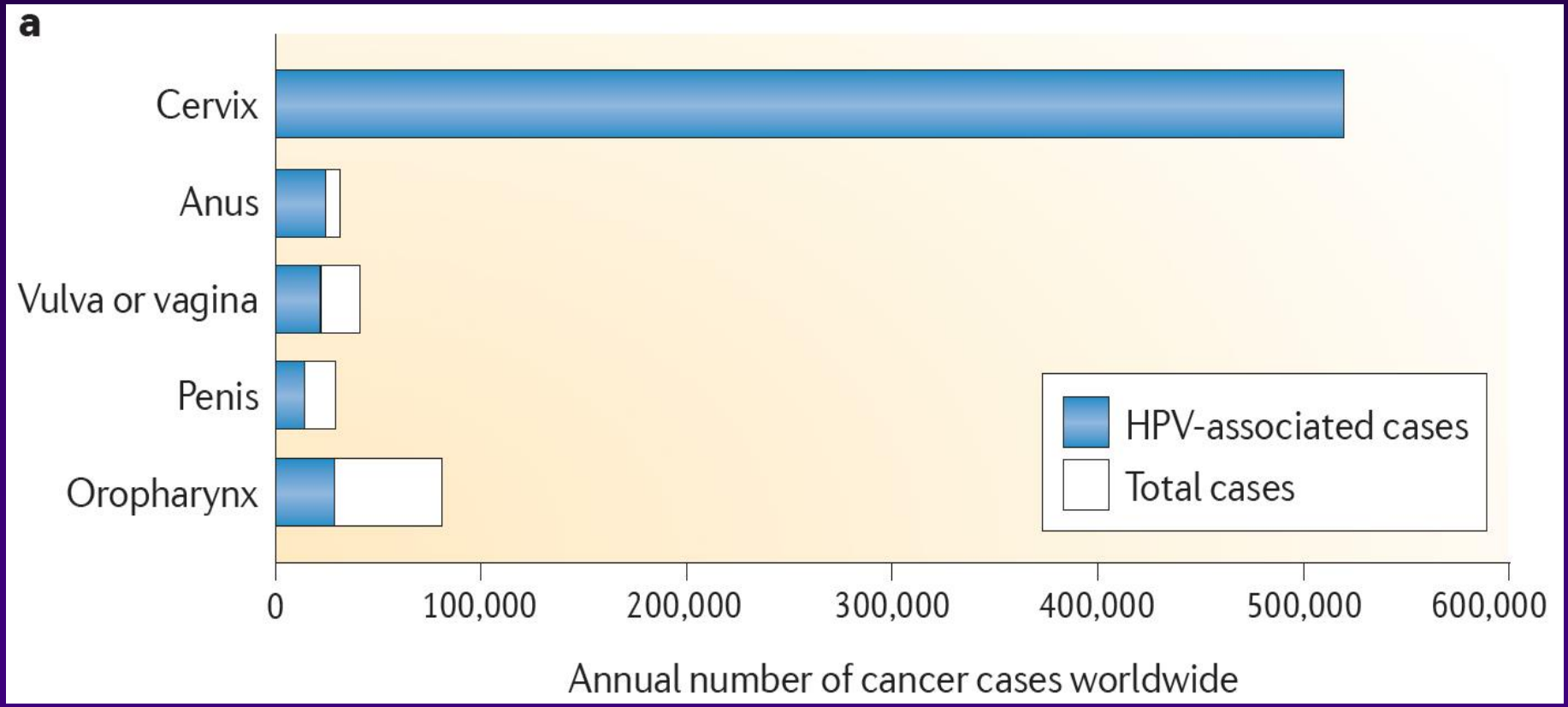






High-risk alpha HPV genotypes

HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39
HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59



Schiller JT, Lowy DR. Nat Rev Microbiol 2012;10:681-92.

Worldwide burden of cancer attributable to HPV by site, country and HPV type

Catherine de Martel, Martyn Plummer, Jerome Vignat and Silvia Franceschi

International Agency for Research on Cancer, Lyon, France

Int J Cancer 2017;141:664–70

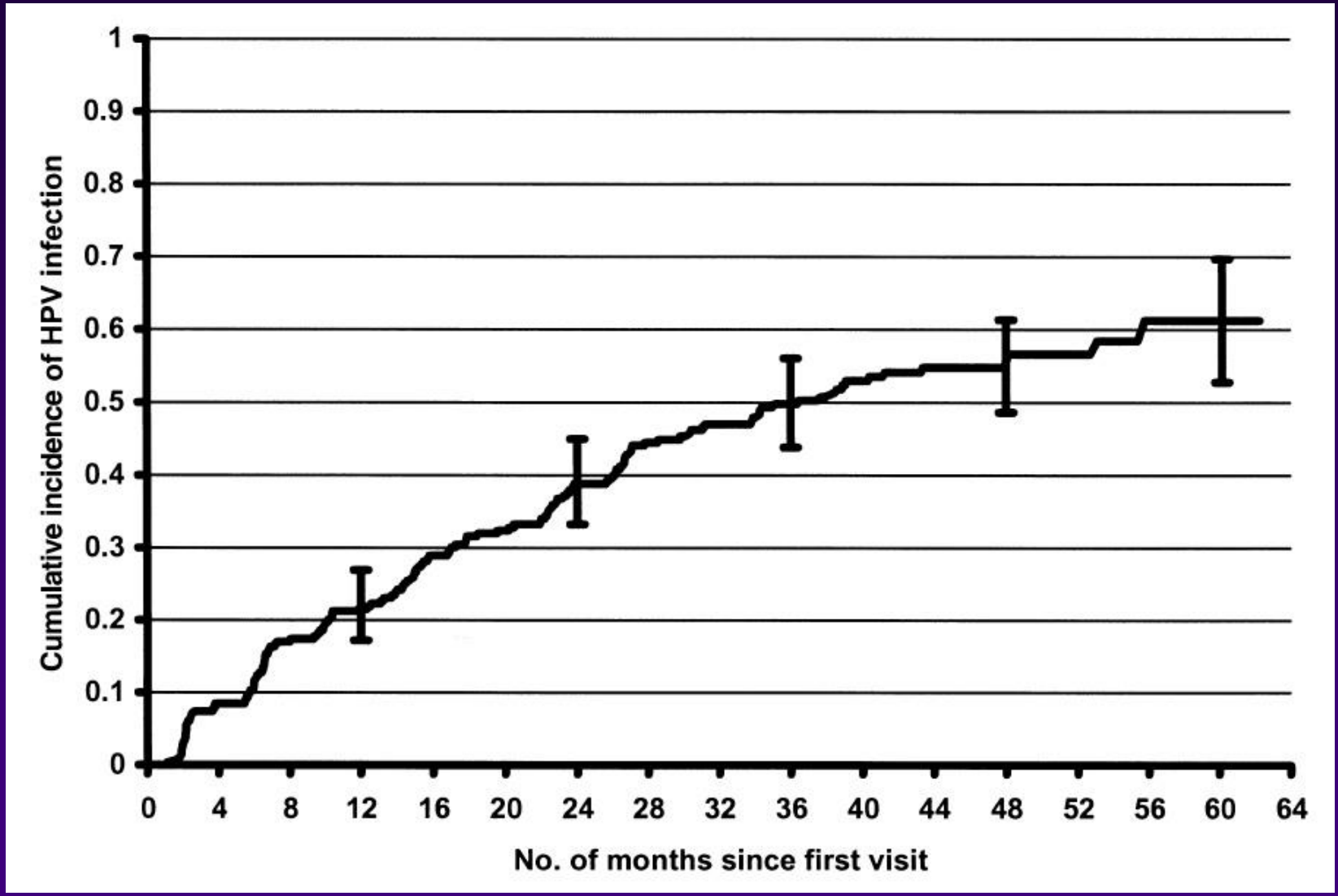
Cancers attributable to HPV:

- 4.5% of all cancers worldwide
- 630,000 new cancer cases per year
- 8.6% of all cancers in women
- 0.8% of all cancers in men

GLOBOCAN 2012 data

Natural history of HPV infection

Cumulative incidence of HPV infection among women sexually active and HPV negative at enrollment in Washington State, 1990–2000



Winer RL et al. Am J Epidemiol 2003; 157:218-26

Age of Acquiring Causal Human Papillomavirus (HPV) Infections: Leveraging Simulation Models to Explore the Natural History of HPV-induced Cervical Cancer

Emily A. Burger,[1,2] Jane J. Kim,[1] Stephen Sy,[1] Philip E. Castle[3,4]

Clin Infect Dis 2017;65:893-9

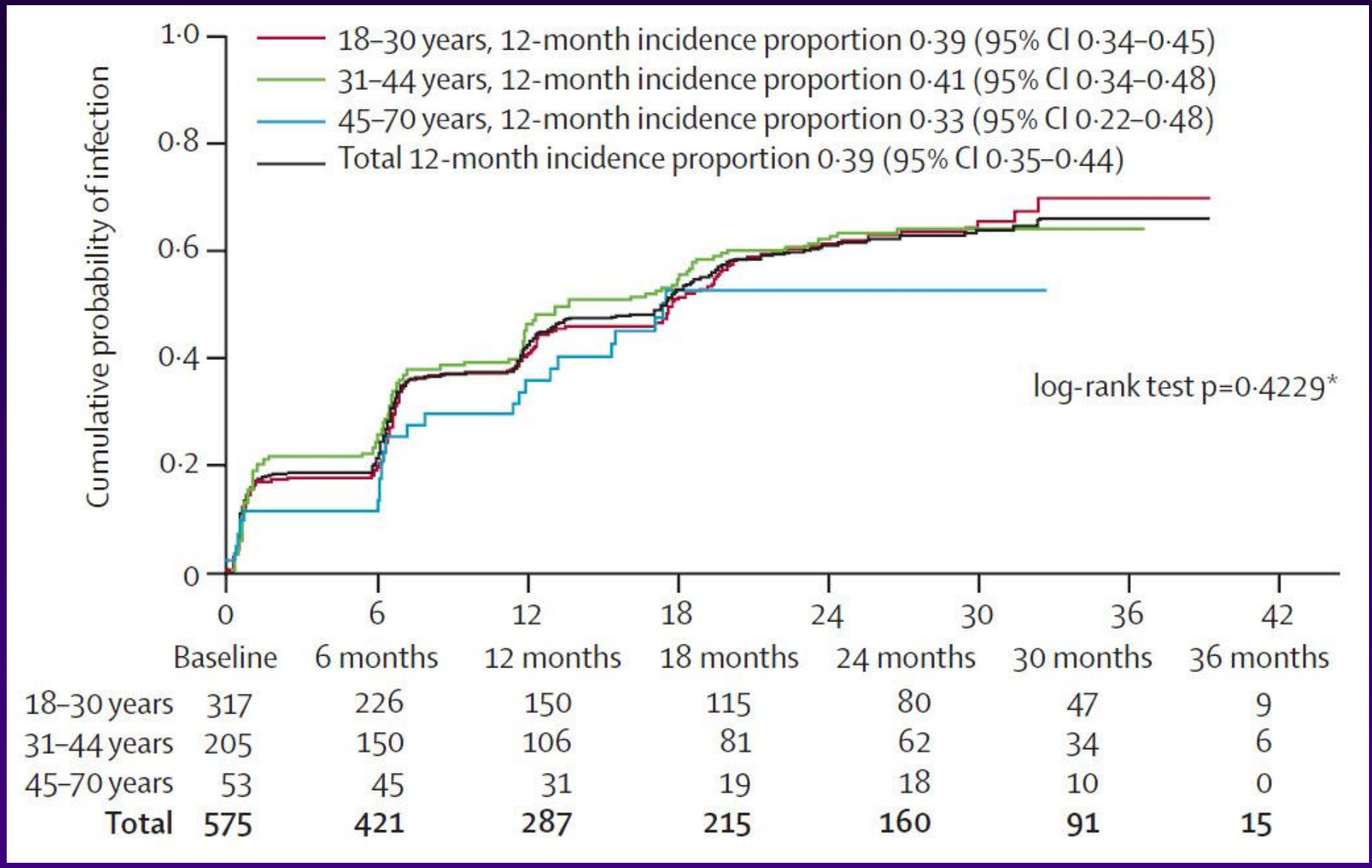
[1]Harvard T.H. Chan School of Public Health, Center for Health Decision Science, Boston, Massachusetts; [2]University of Oslo, Department of Health Management and Health Economics, Oslo, Norway; [3]Albert Einstein College of Medicine, Department of Epidemiology and Population Health, Bronx, New York; [4]Global Coalition Against Cervical Cancer, Arlington, Virginia.

50% of women acquired their causal HPV infection by ages 20.6 (range: 20.1–21.1) years

75% of women acquired their causal HPV infection by ages 30.6 (range: 29.6–31.6) years

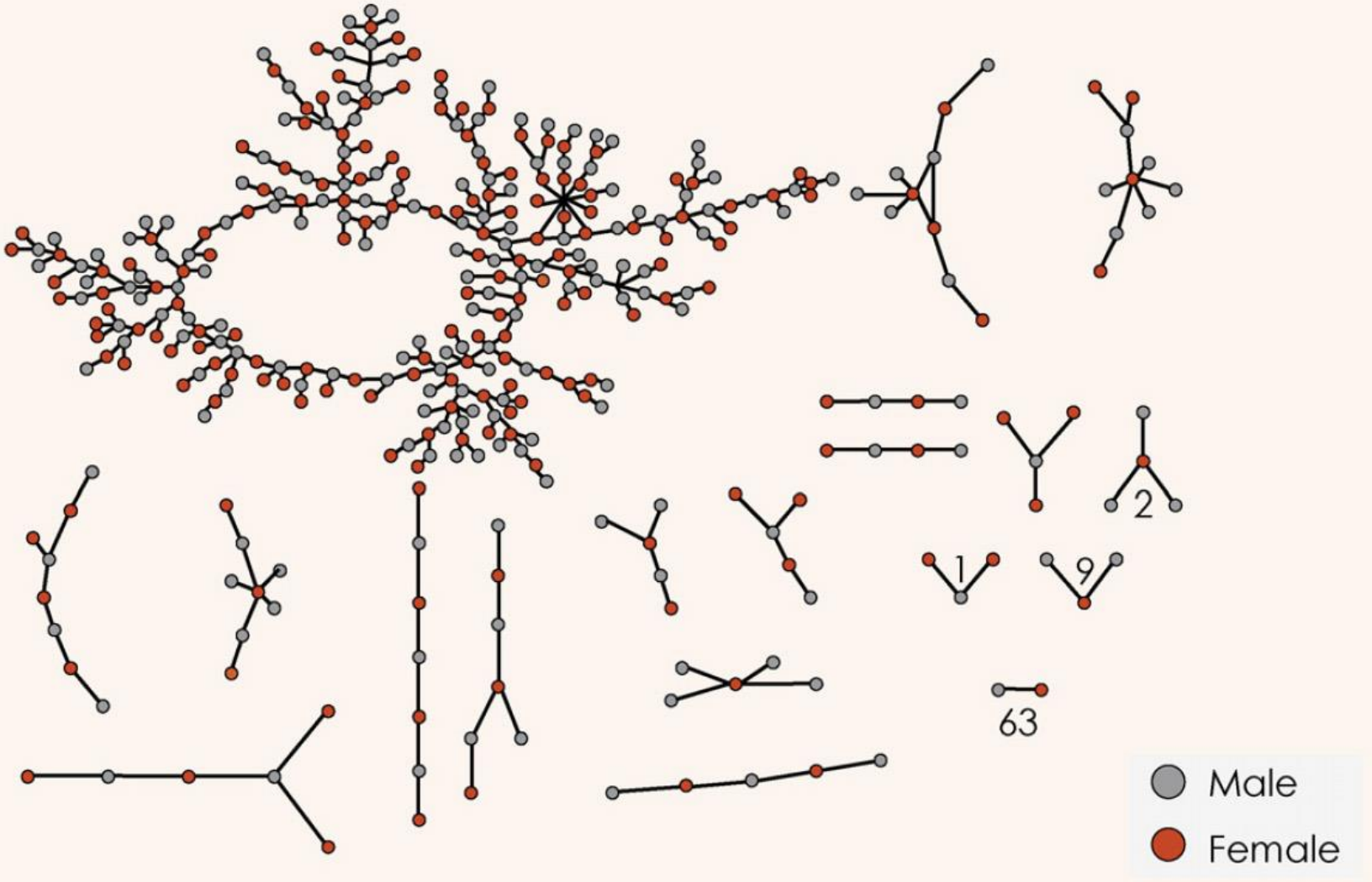
HPV16 infections were acquired at an earlier age

although new HPV infections can occur throughout a woman's lifetime, only a small proportion are acquired in mid-adult women and are vaccine-preventable



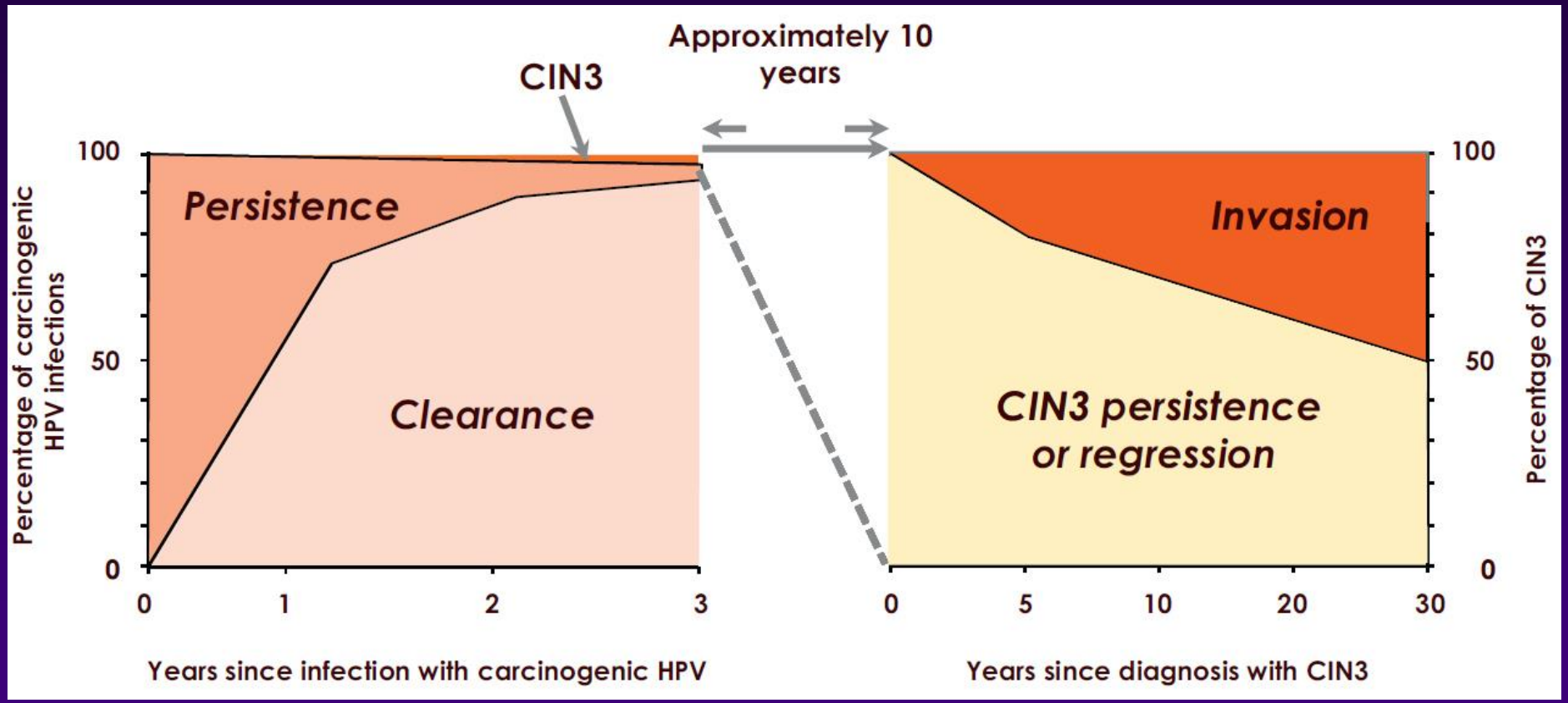
Giuliano AR et al. Lancet 2011; 377: 932-40.

Network structure linking 573 secondary school students in a romantic or sexual relationship with another student at 'Jefferson High', USA.

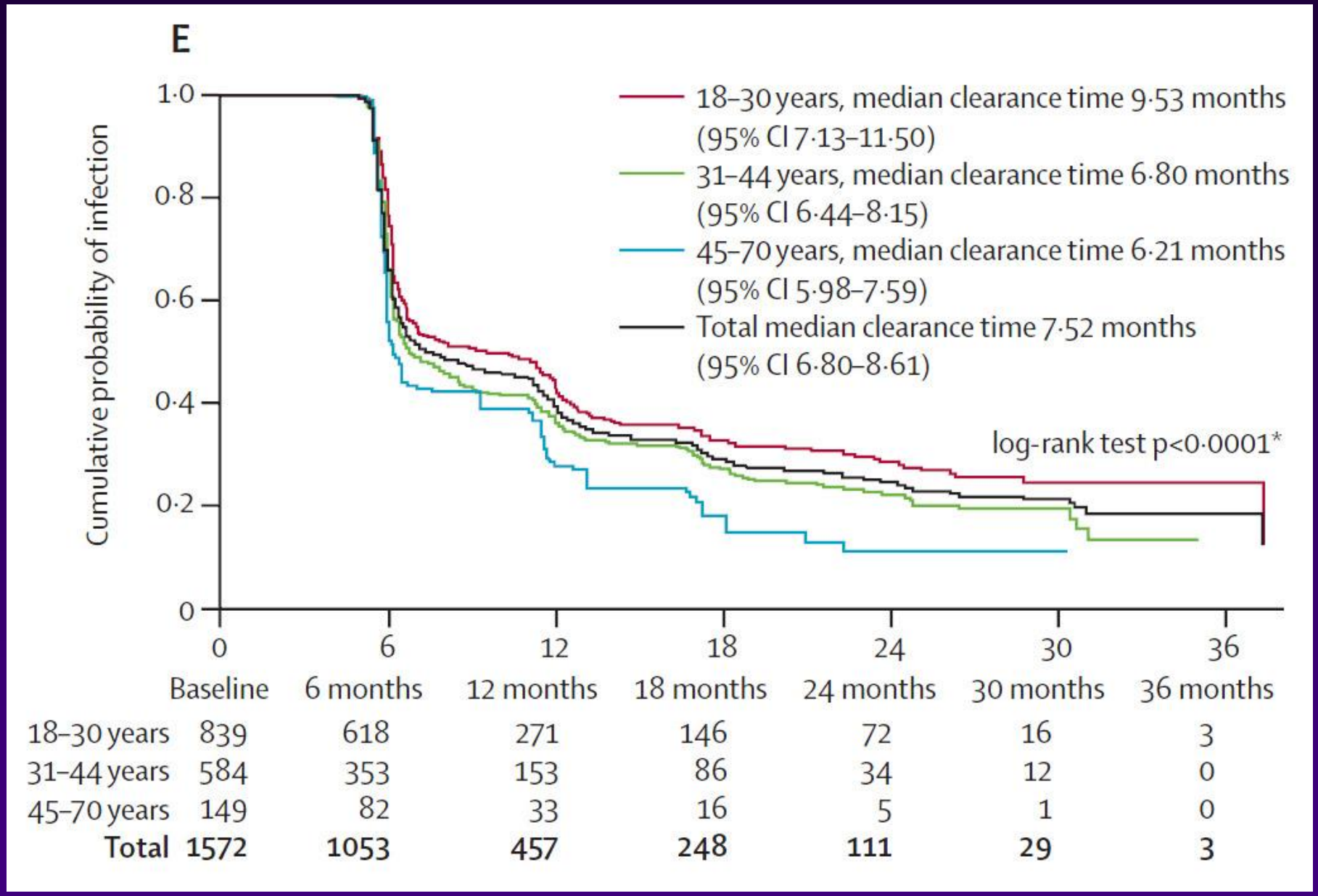


Bearman PS, et al. Am J Sociol 2004;110:44–91.

Natural history of HPV infection

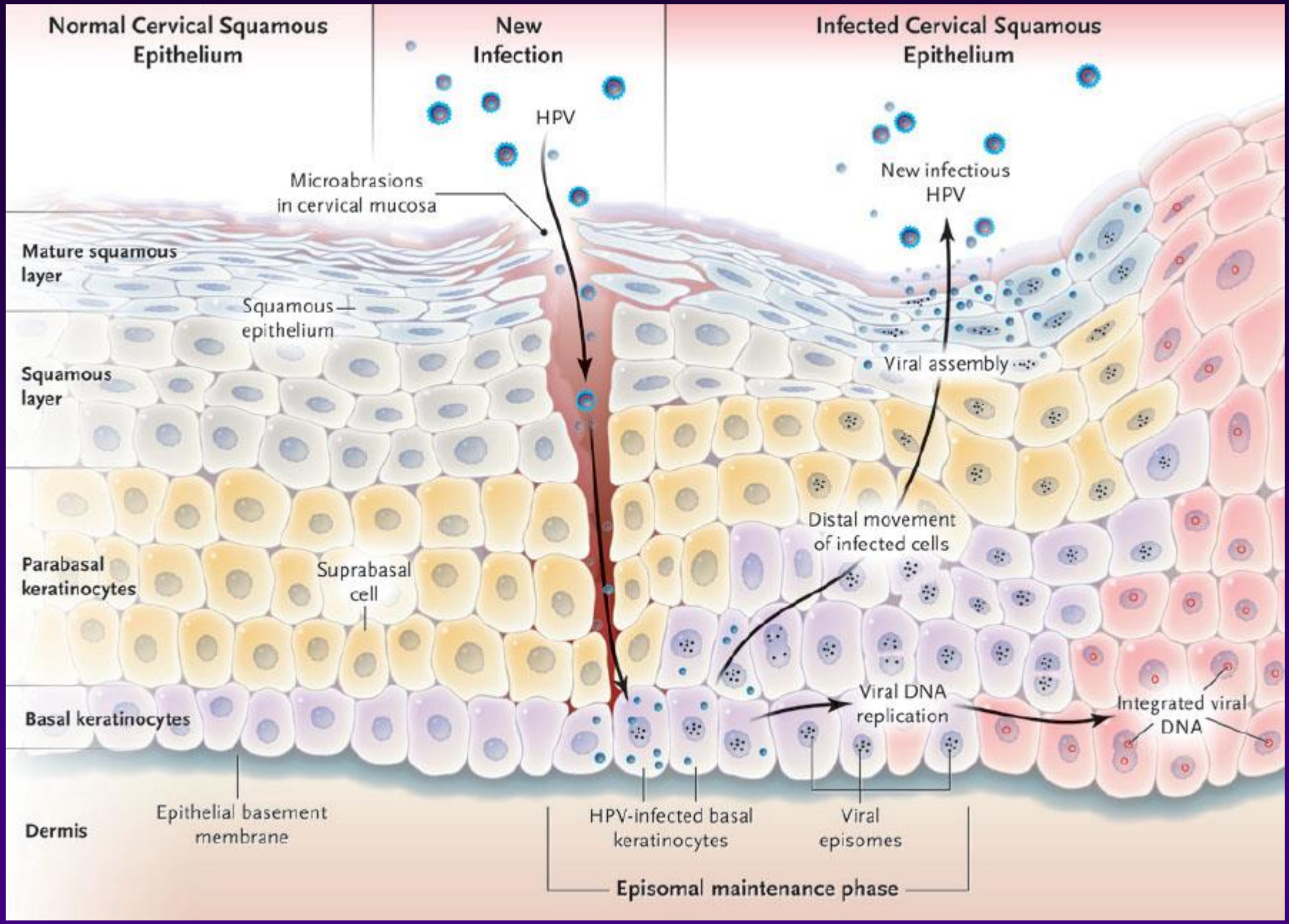


Moscicki AB et al. Vaccine 30S (2012) F24– F33

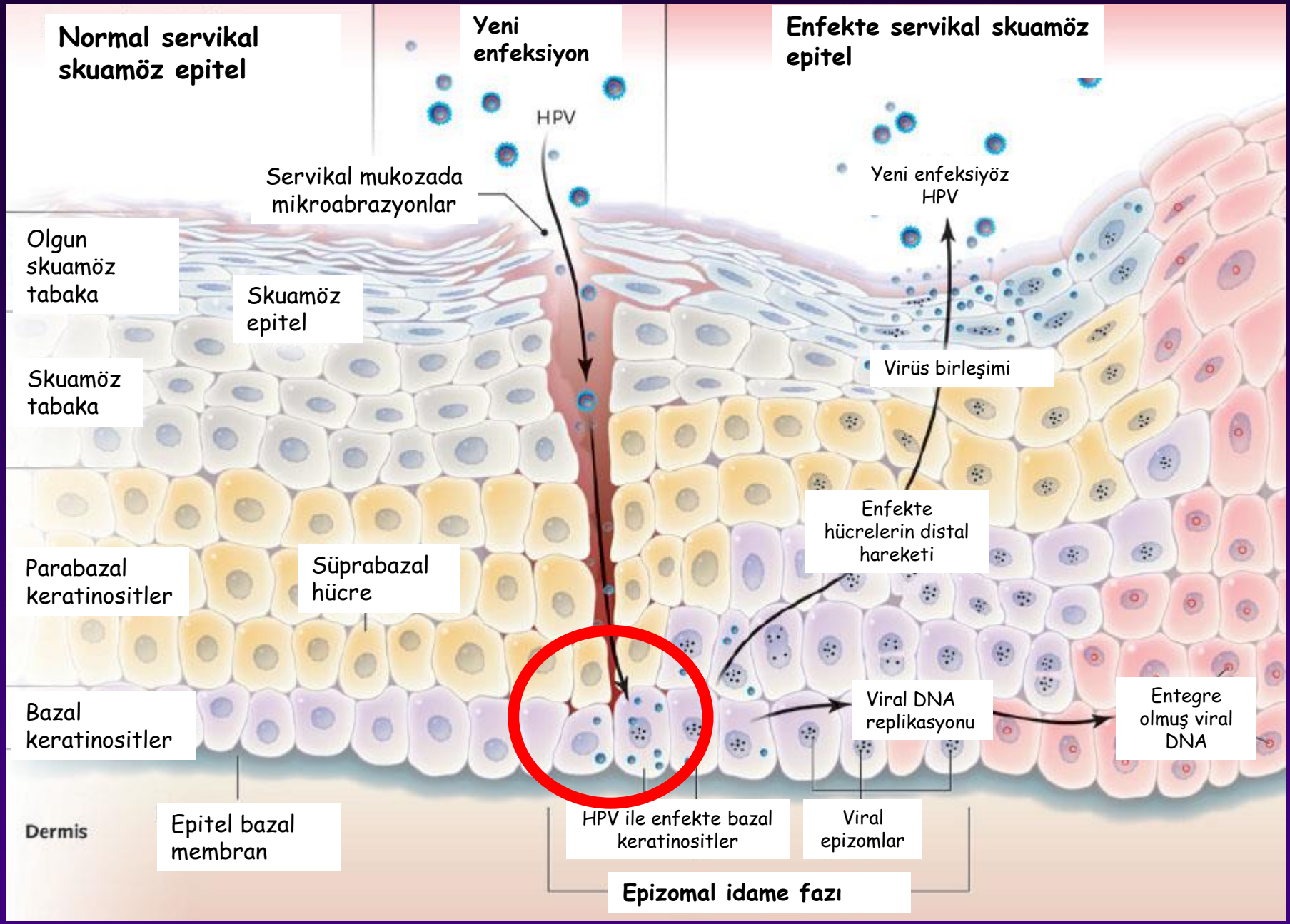


Giuliano AR et al. Lancet 2011; 377: 932-40.

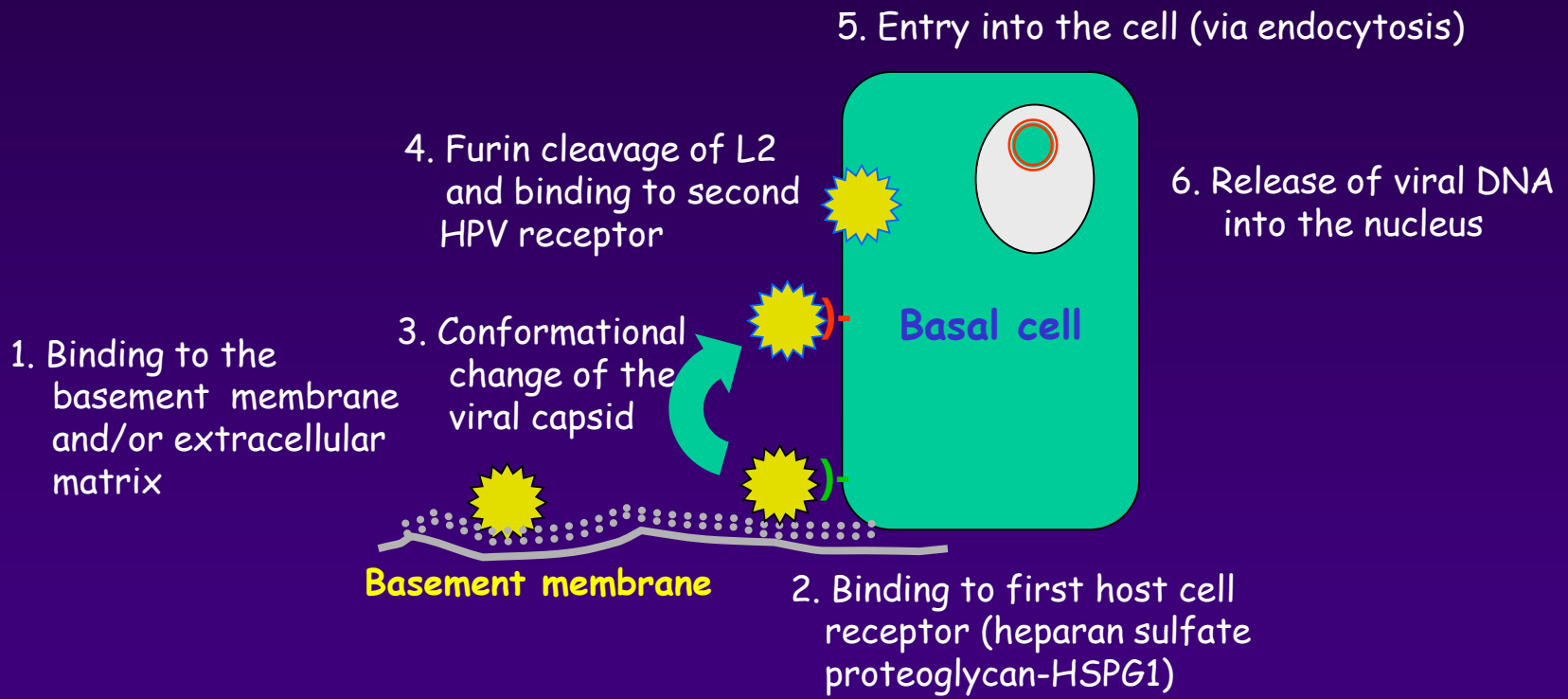
Patogenesis of HPV infection



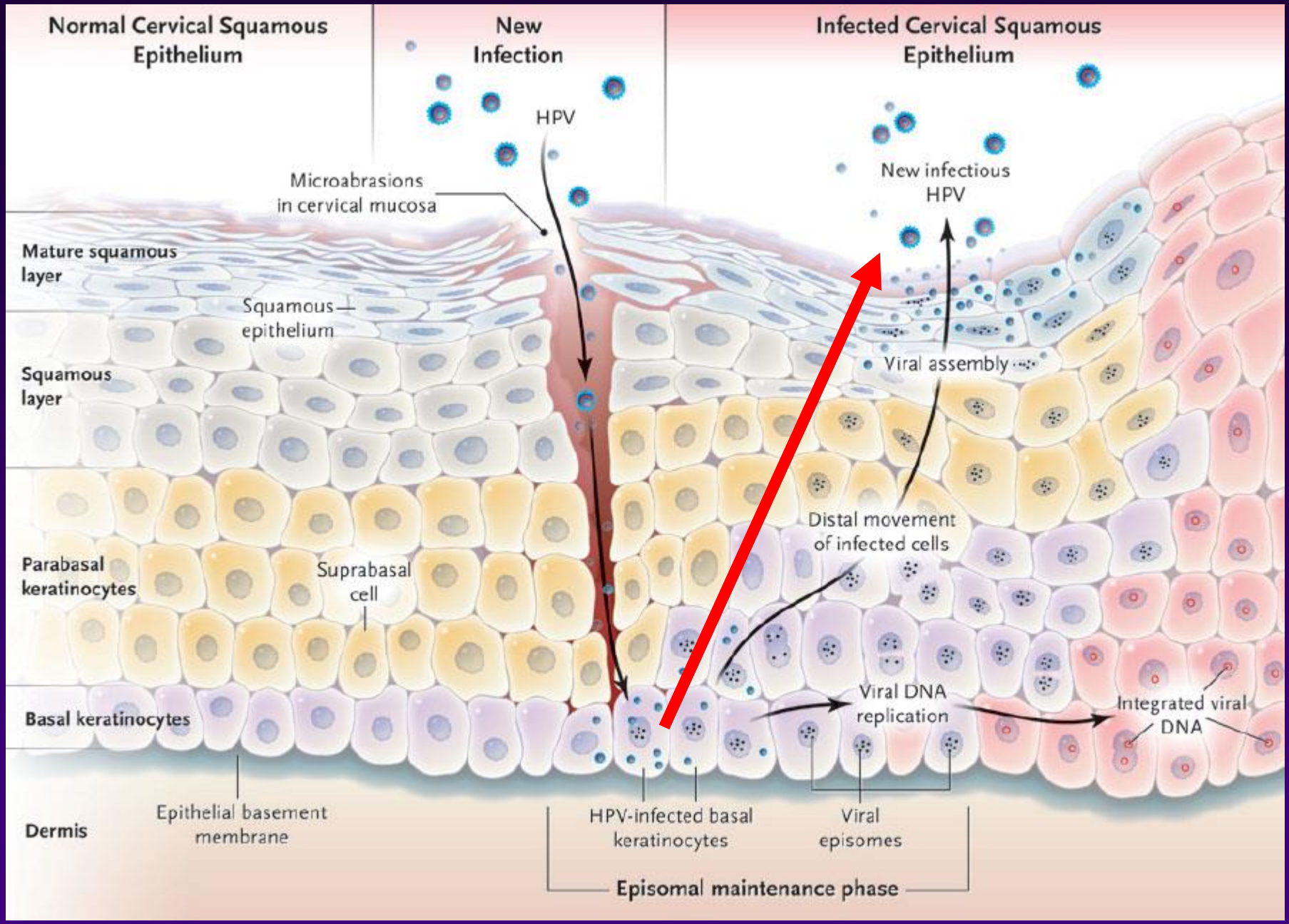
Kahn JA. N Engl J Med 2009; 361:271-8.



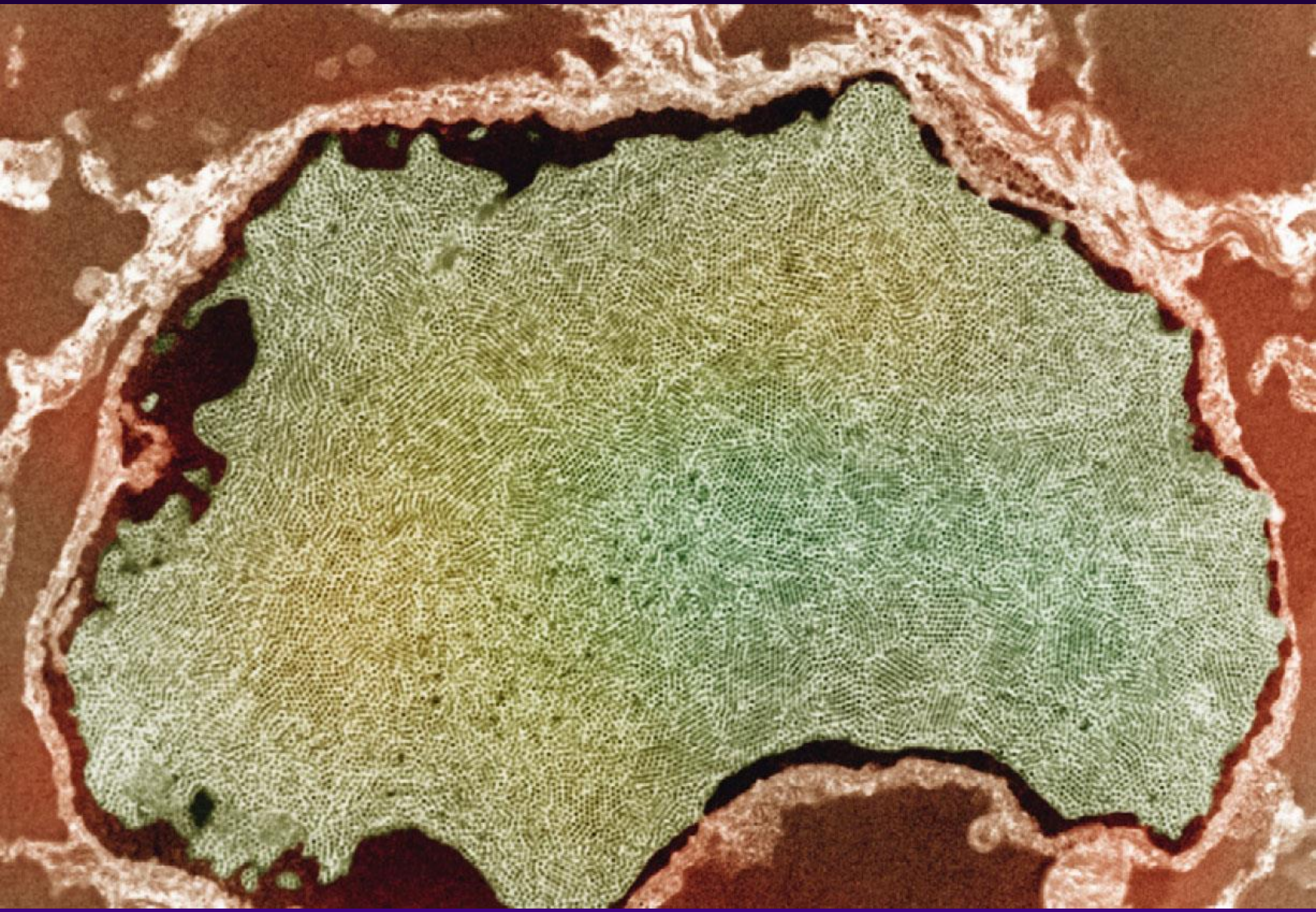
Kahn JA. N Engl J Med 2009; 361:271-8.

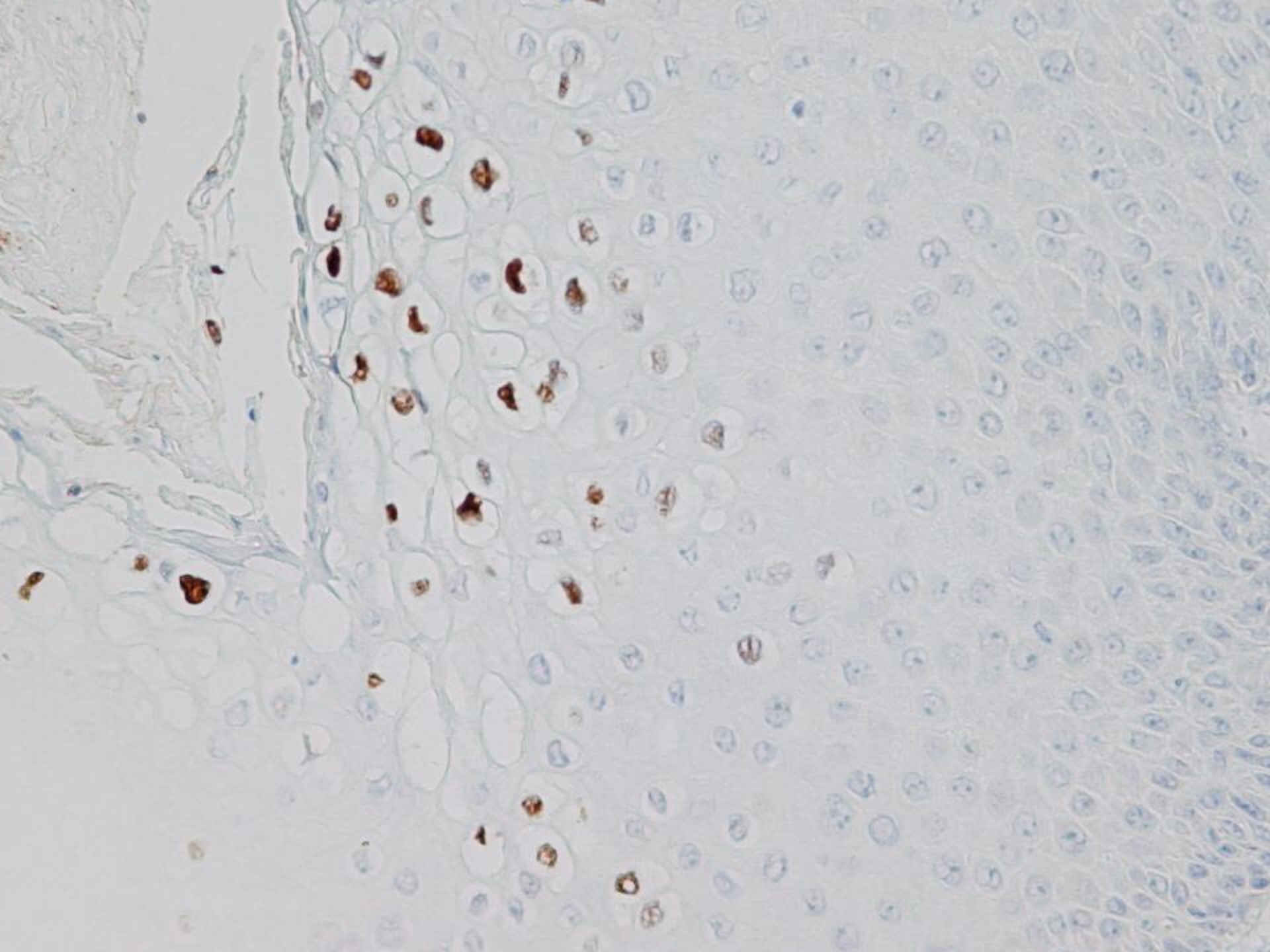


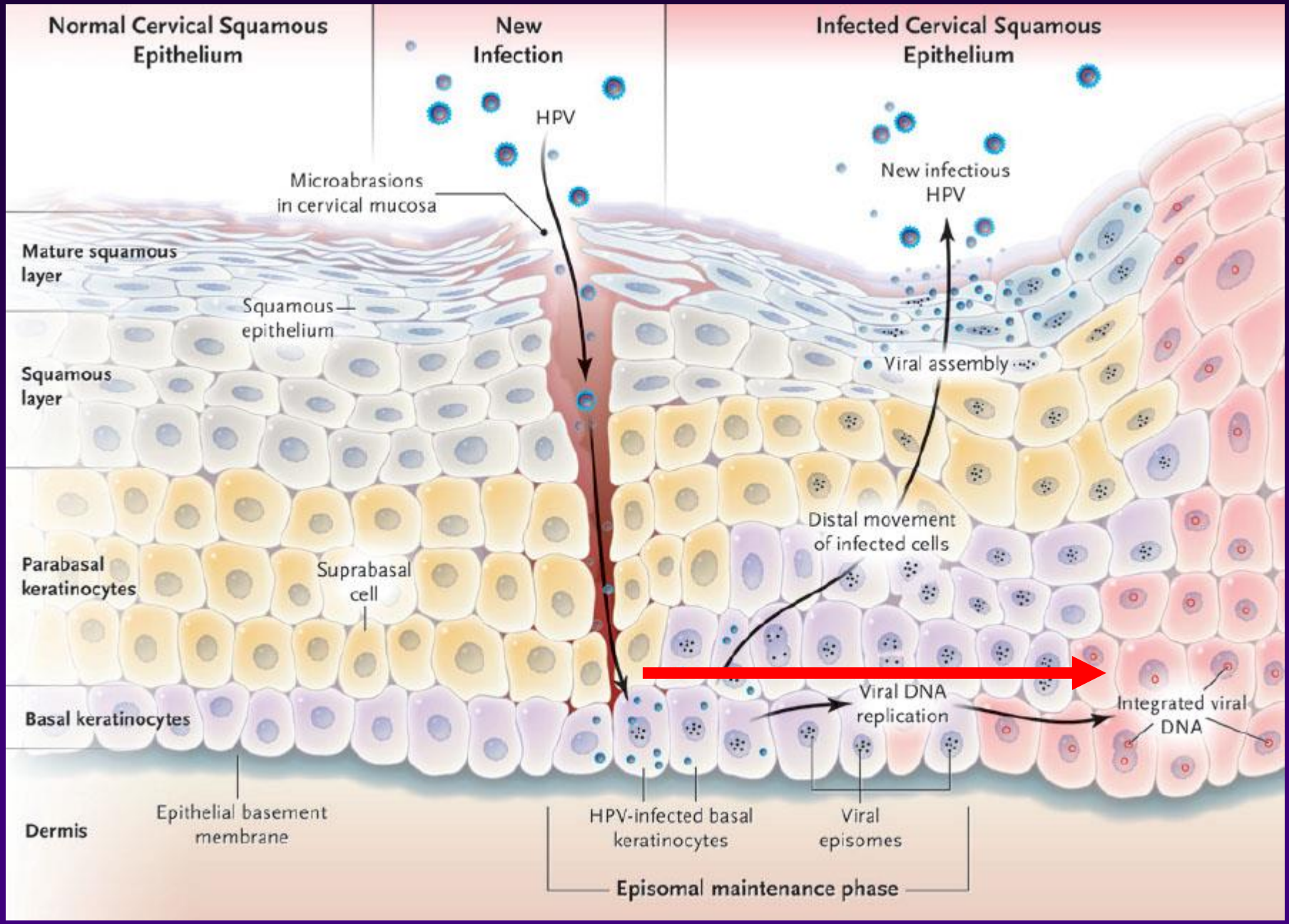
Sapp M, Day PM. Virology 2009;384: 400-9.



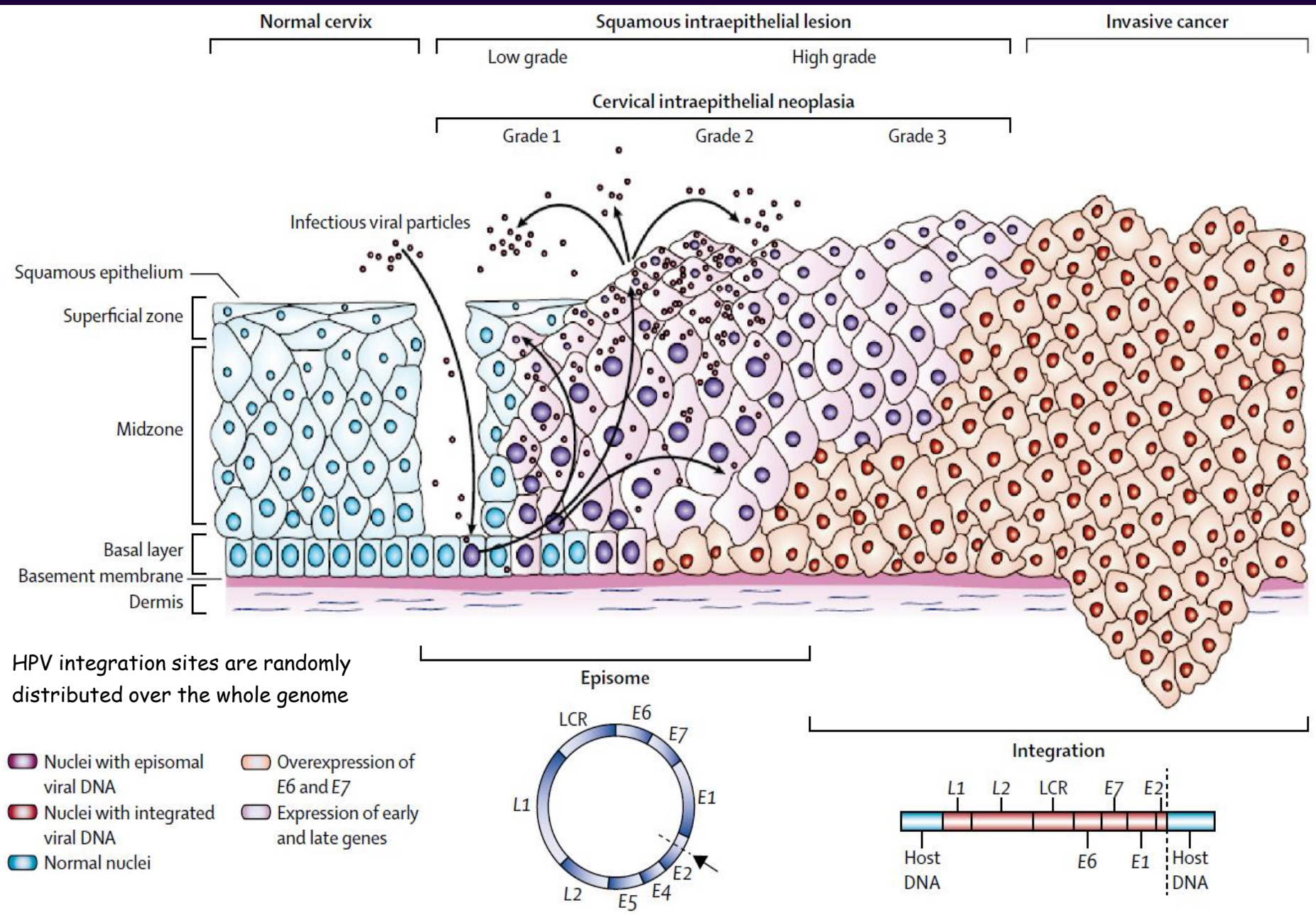
Kahn JA. N Engl J Med 2009; 361:271-8.



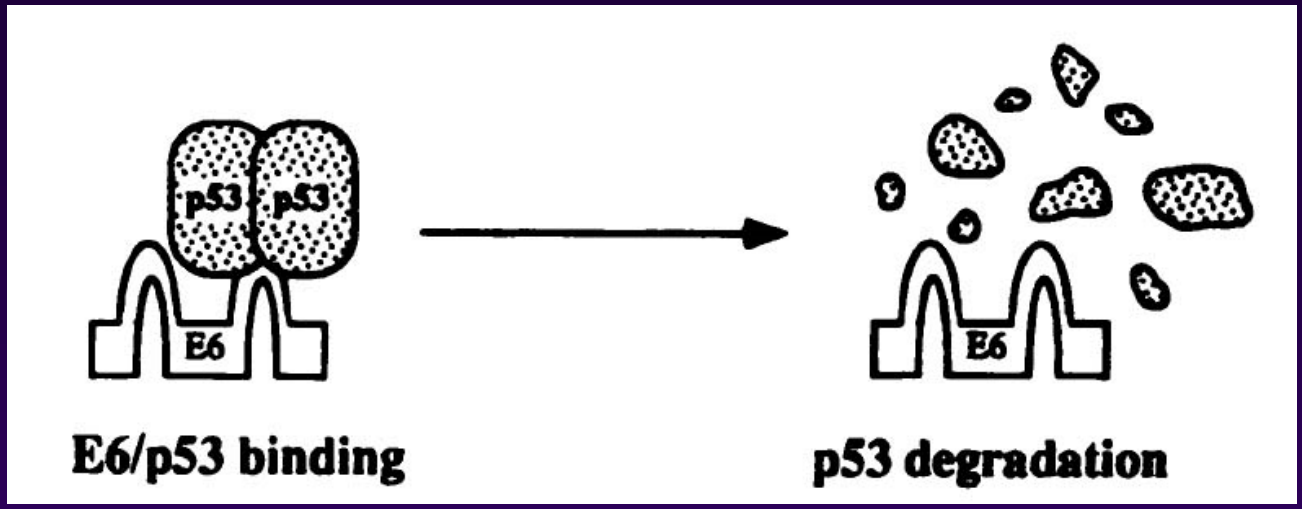


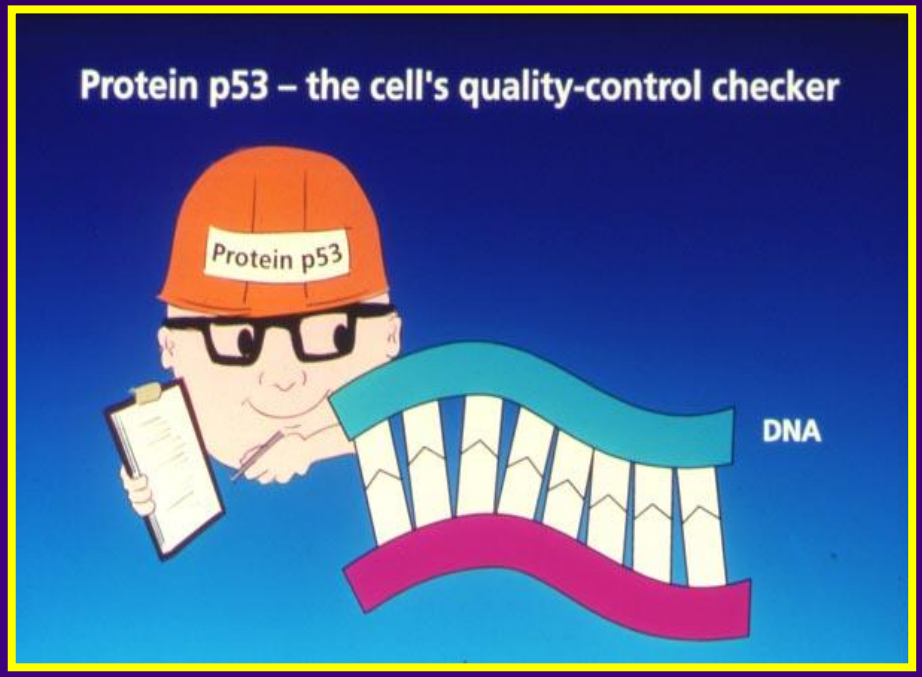


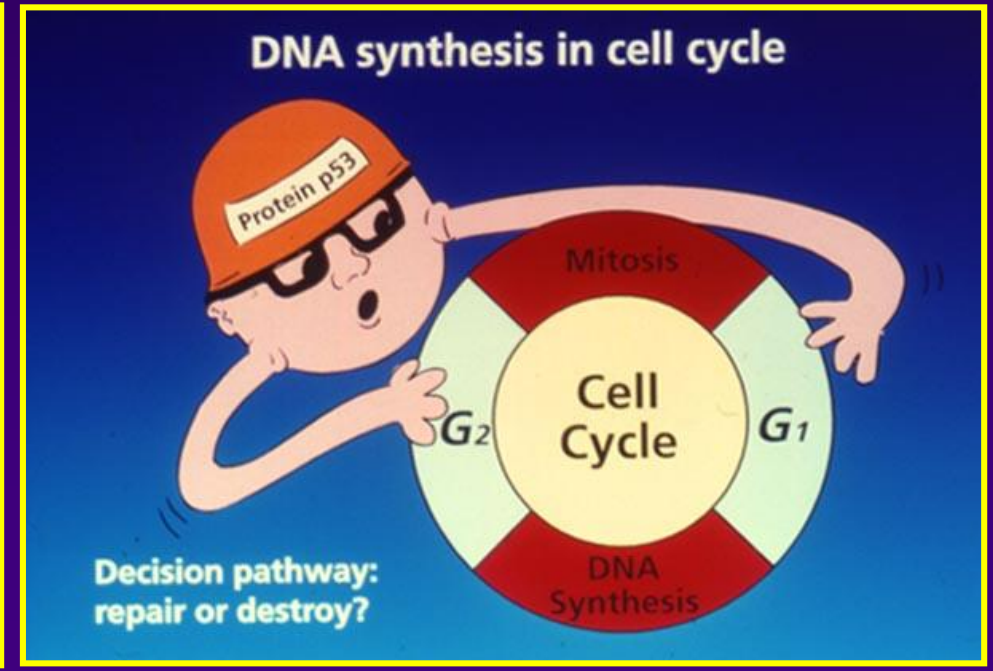
Kahn JA. N Engl J Med 2009; 361:271-8.

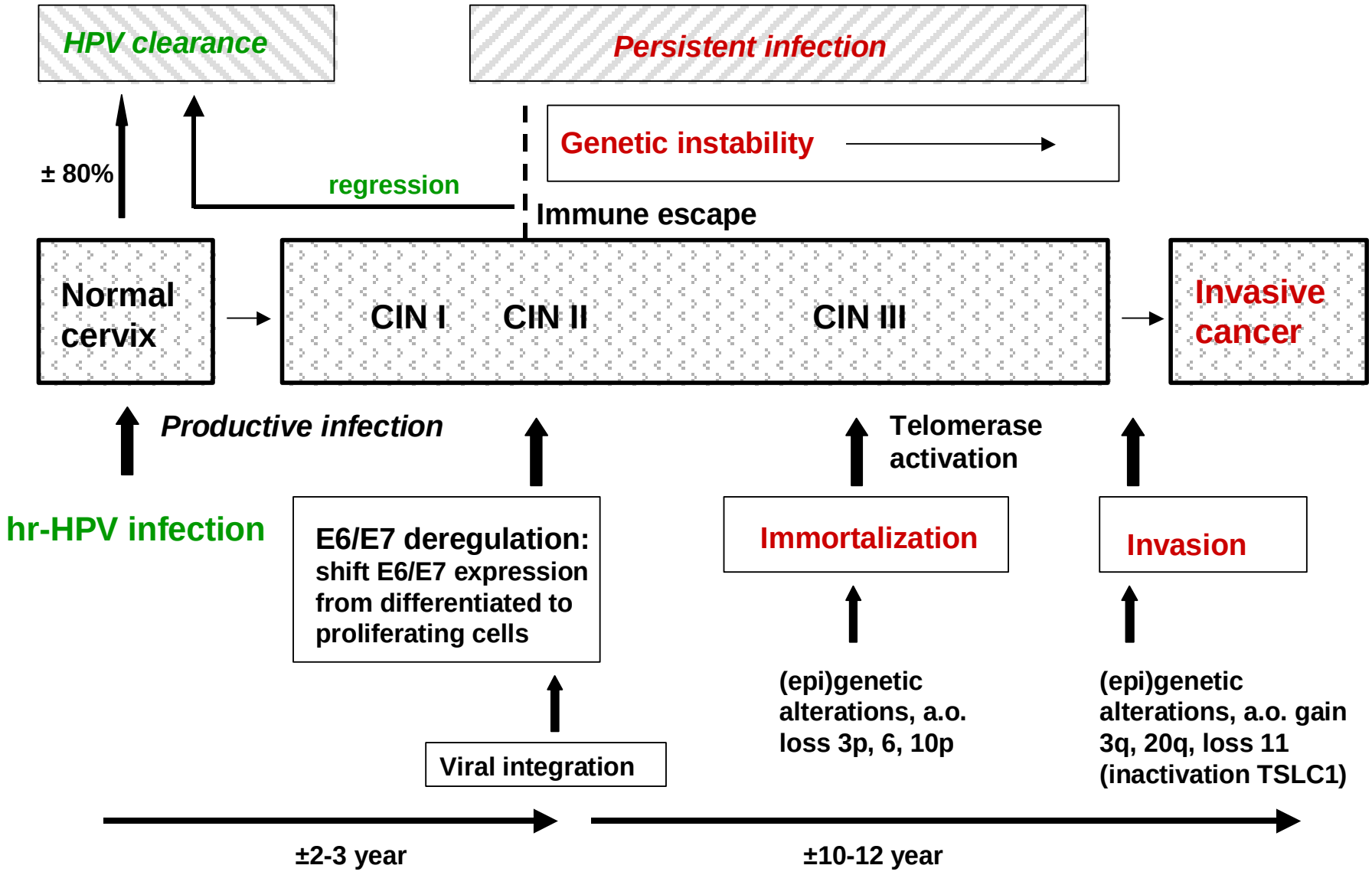


Crosbie EJ et al. Lancet 2013; 382: 889–899.


p53
p53
E6
E6
E6/p53 binding
p53 degradation


Protein p53 – the cell's quality-control checker
Protein p53
DNA


DNA synthesis in cell cycle
Protein p53
Mitosis
Cell Cycle
G2
G1
DNA Synthesis
Decision pathway: repair or destroy?



J Clin Virol 2005; 32S: S25-S33

Preliminary Communication

Potential Mechanisms for Cancer Resistance in Elephants and Comparative Cellular Response to DNA Damage in Humans

Lisa M. Abegglen, PhD; Aleah F. Caulin, PhD; Ashley Chan, BS; Kristy Lee, PhD; Rosann Robinson, BS; Michael S. Campbell, PhD; Wendy K. Kiso, PhD; Dennis L. Schmitt, DVM, PhD; Peter J. Waddell, PhD; Srividya Bhaskara, PhD; Shane T. Jensen, PhD; Carlo C. Maley, PhD; Joshua D. Schiffman, MD

JAMA 2015;314:1850-60

Compared with other mammalian species, elephants appeared to have a lower-than-expected rate of cancer, potentially related to multiple copies of *TP53*.

While humans have 1 copy (2 alleles) of *TP53*, African elephants have at least 20 copies (40 alleles), including 19 retrogenes (38 alleles) with evidence of transcriptional activity measured by reverse transcription polymerase chain reaction

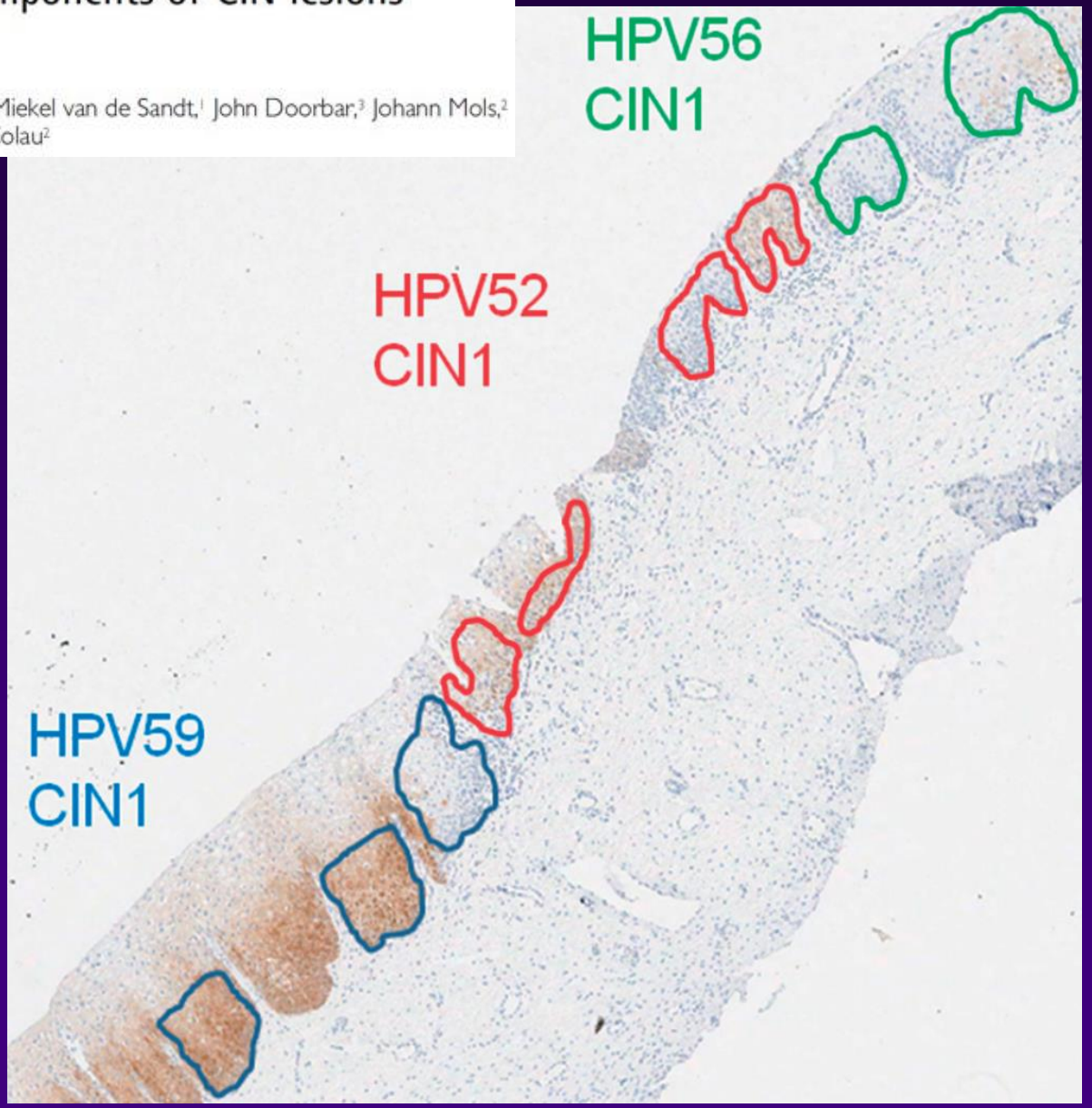
In response to DNA damage, elephant lymphocytes underwent p53-mediated apoptosis at higher rates than human lymphocytes proportional to *TP53* status.

Journal of Pathology
J Pathol 2012; **227:** 62–71
Published online 17 February 2012 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.3970

ORIGINAL PAPER

One virus, one lesion—individual components of CIN lesions contain a specific HPV type

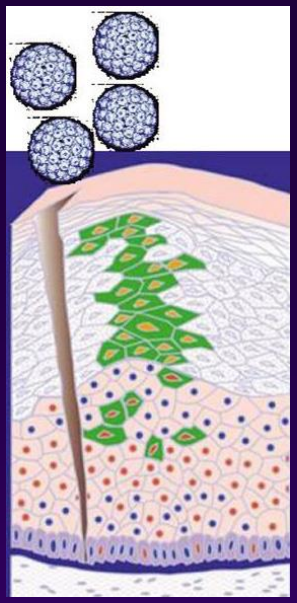
Wim Quint,[1*†] David Jenkins,[2‡‡] Anco Molijn,[1] Linda Struijk,[1] Miekel van de Sandt,[1] John Doorbar,[3] Johann Mols,[2] Christine Van Hoof,[4] Karin Hardt,[2] Frank Struyf[2] and Brigitte Colau[2]



Imunology of HPV infection

HPV

Viral characteristics



exclusively intraepithelial pathogens (avoidance of antigen presentation)

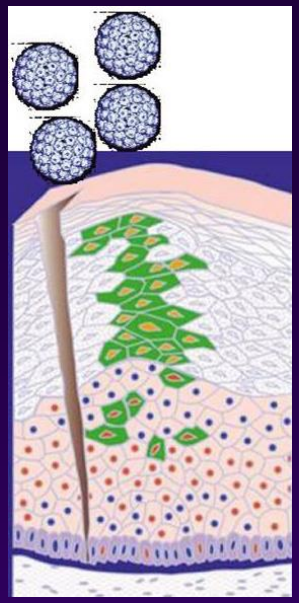
do not lyse keratinocytes (no cell death, no inflammation)

no blood-borne phase of the HPV life cycle

only minimal amounts of replicating virus are exposed to immune system

HPV

Viral characteristics

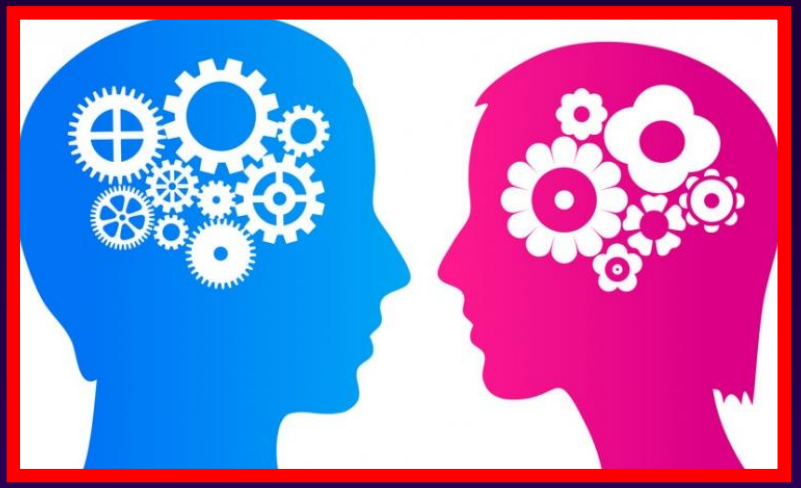


HPV encode proteins that inhibit apoptosis and delay the differentiation program of the infected keratinocyte

HPV downregulate interferon responses and disable the epithelial LCs

the virus is practically invisible to the host who remains ignorant of the pathogen for long periods of time

Natural HPV infection



women:

- 54%–69% seroconvert
- low-level antibodies
- partial protection against reinfection

Redetection of Cervical Human Papillomavirus Type 16 (HPV16) in Women With a History of HPV16

The Journal of Infectious Diseases 2013;208:403–12

Anna-Barbara Moscicki,[1] Yifei Ma,[1] Sepideh Farhat,[1] Teresa M. Darragh,[2] Michael Pawlita,[4] Denise A. Galloway,[5,6] and Stephen Shiboski[3]

[1]Department of Pediatrics, School of Medicine, [2]Department of Pathology, and [3]Department of Epidemiology and Biostatistics, University of California, San Francisco; [4]Research Program Infection and Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany; [5]Department of Microbiology, University of Washington, Seattle; and [6]Divisions of Human Biology and Public Health Sciences, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Washington

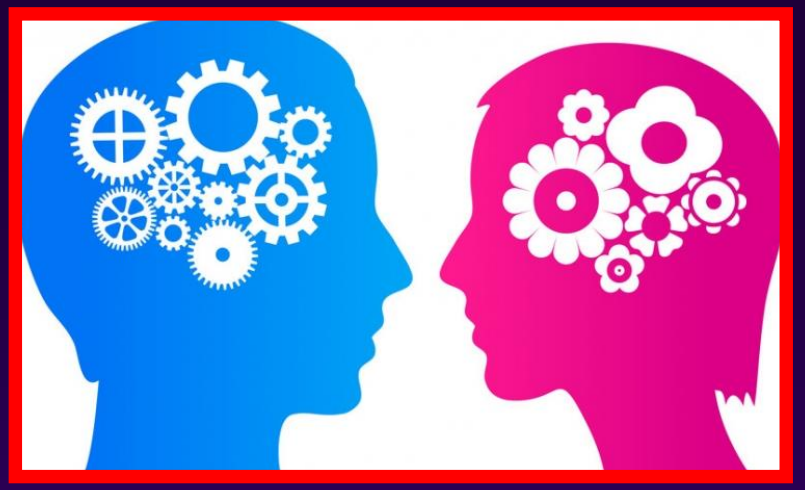
Background. The purpose of this study was to examine the rate of and risks for cervical human papillomavirus type 16 (HPV16) redetection in women with documented or suspected HPV16 infection.

Methods. A convenience sample of women aged 13–21 years were seen at 4-month intervals for HPV DNA testing and cytology. Serum samples were obtained at baseline and annually.

Results. A total of 1543 women entered the study. Of the 295 women with detection of HPV16 DNA and subsequent clearance, 18.1% had HPV16 redetected by 8.5 years (88% cleared this second detection by 3 years). Of the 247 women who had antibodies to HPV16 and were HPV16 DNA negative at baseline, 15.3% had HPV16 redetected by year 5. Risks for redetection included douching, current use of medroxyprogesterone, reporting >1 sex partner or having a new sex partner, and having a sexually transmitted infection. Development of cervical intraepithelial neoplasia 2/3 was rare in women with redetection, except for those with prevalent HPV16 infection.

Conclusions. Reappearance of HPV16 DNA was observed in 18% of women. Most are associated with sexual exposure and appear benign. Interpretation of the studies is more complex in women with prevalent infections as it appears that this small subset reflects women with persistence already present at entry.

Natural HPV infection



women:

- 54%–69% seroconvert
- low-level antibodies
- partial protection against reinfection

men:

- 7%–10% seroconvert
- low-level antibodies
- no protection against reinfection

BUT: nearly 100% seroconversion following HPV vaccination in both genders !

Why are HPV vaccines "better" than nature ??

Natural infection

- no viraemia, poor access of virus to lymph nodes

HPV vaccines

- delivered intramuscularly
- rapid access of VLPs to blood vessels and local lymph nodes

Why are HPV vaccines "better" than nature ??

Natural infection

– no viraemia, poor access of virus to lymph nodes

HPV vaccines

- delivered intramuscularly
- rapid access of VLPs to blood vessels and local lymph nodes

BONUS

VLPs are very immunogenic:

- display many neutralising epitopes (more than native virion)
- induce good T-cell helper responses for B-cells

long lived plasma cells and not memory B or T cells key immune effectors

Diagnosis of clinically relevant HPV infections

WHO leads the way towards the elimination of cervical cancer as a public health concern

September 2018 | Cervical cancer is a grave threat to women's health and lives, and globally, one woman dies of cervical cancer every two minutes. This suffering is unacceptable, particularly as cervical cancer is largely preventable.

Cervical cancer screening and prevention, Zambia

secondary prevention (screening)

(cytology, HPV, cytology + HPV)

+

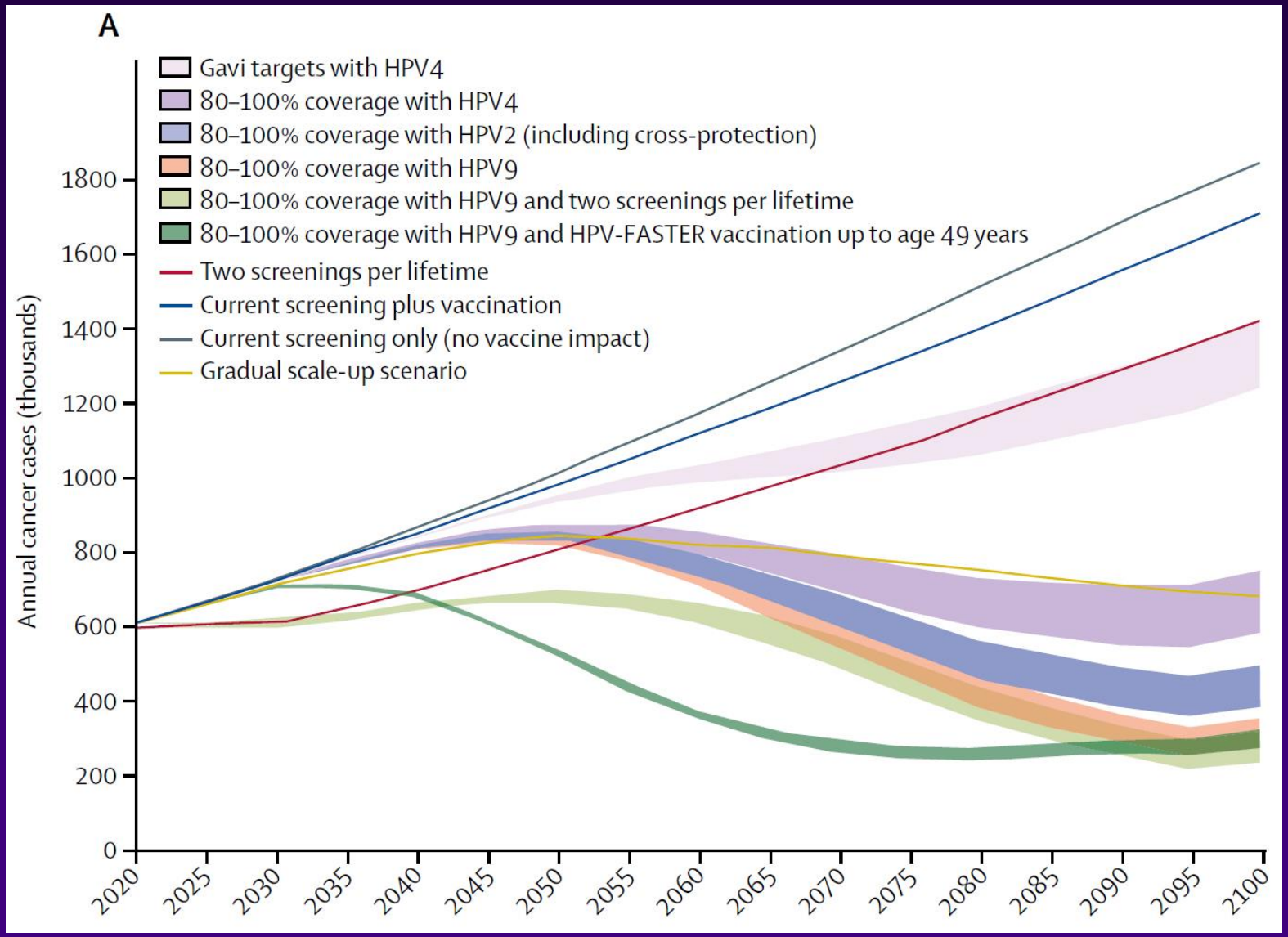
primary prevention (vaccination)

secondary and primary prevention act additively by intervening at different points in the natural history of cervical cancer and imply actions in women of different ages

Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020–99: a modelling study

Lancet Oncol 2019;20:394-407

Kate T Simms, Julia Steinberg, Michael Caruana, Megan A Smith, Jie-Bin Lew, Isabelle Soerjomataram, Philip E Castle, Freddie Bray, Karen Canfell



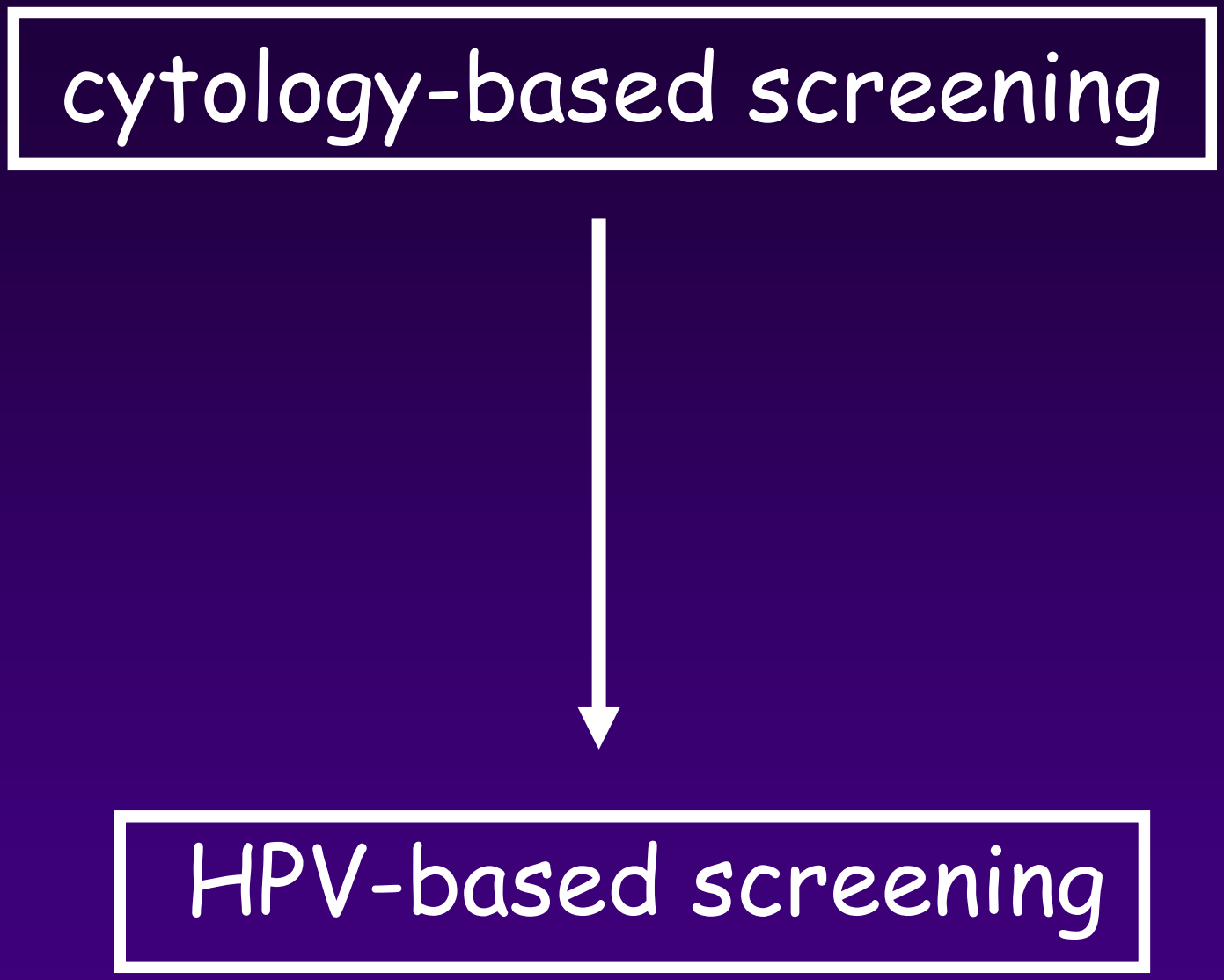
secondary prevention (screening)

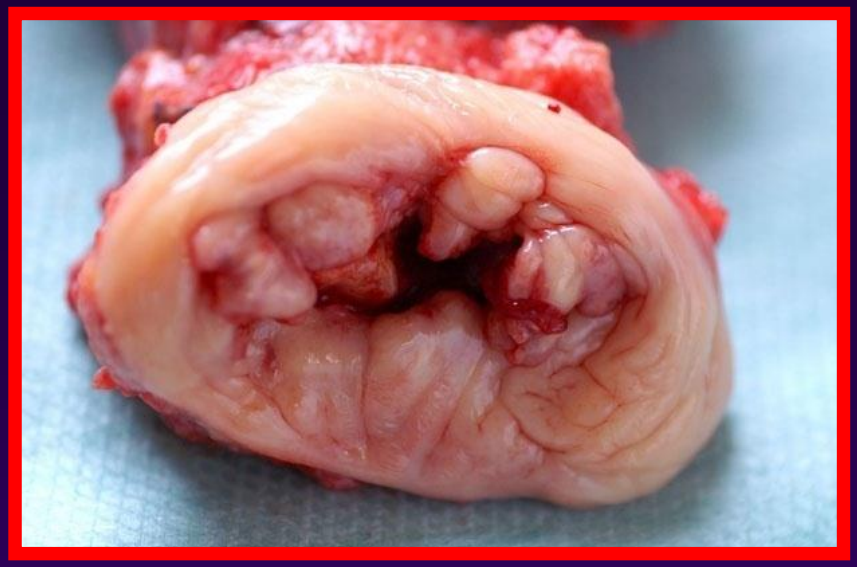
(cytology, HPV, cytology + HPV)

The major goal of cervical screening programmes is to find pre-cancers that can be treated to prevent invasive cancers.


K.13483/08
K.13475

population-based
&
organised
&
high coverage
&
high quality cytology


cytology-based screening
HPV-based screening



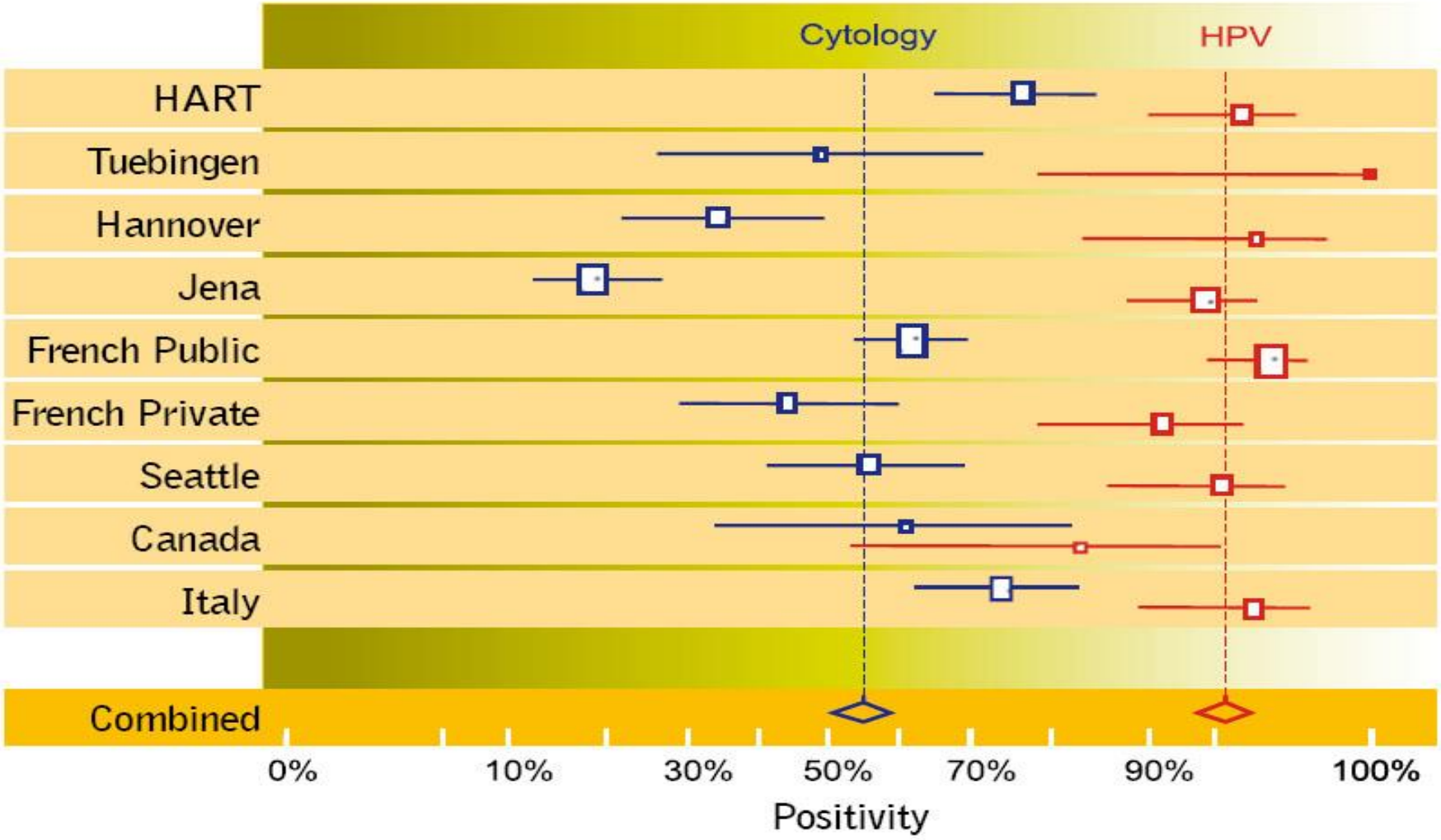
HPV DNA is found in virtually all cases of cervical cancer

HPV is a necessary cause of cervical cancer

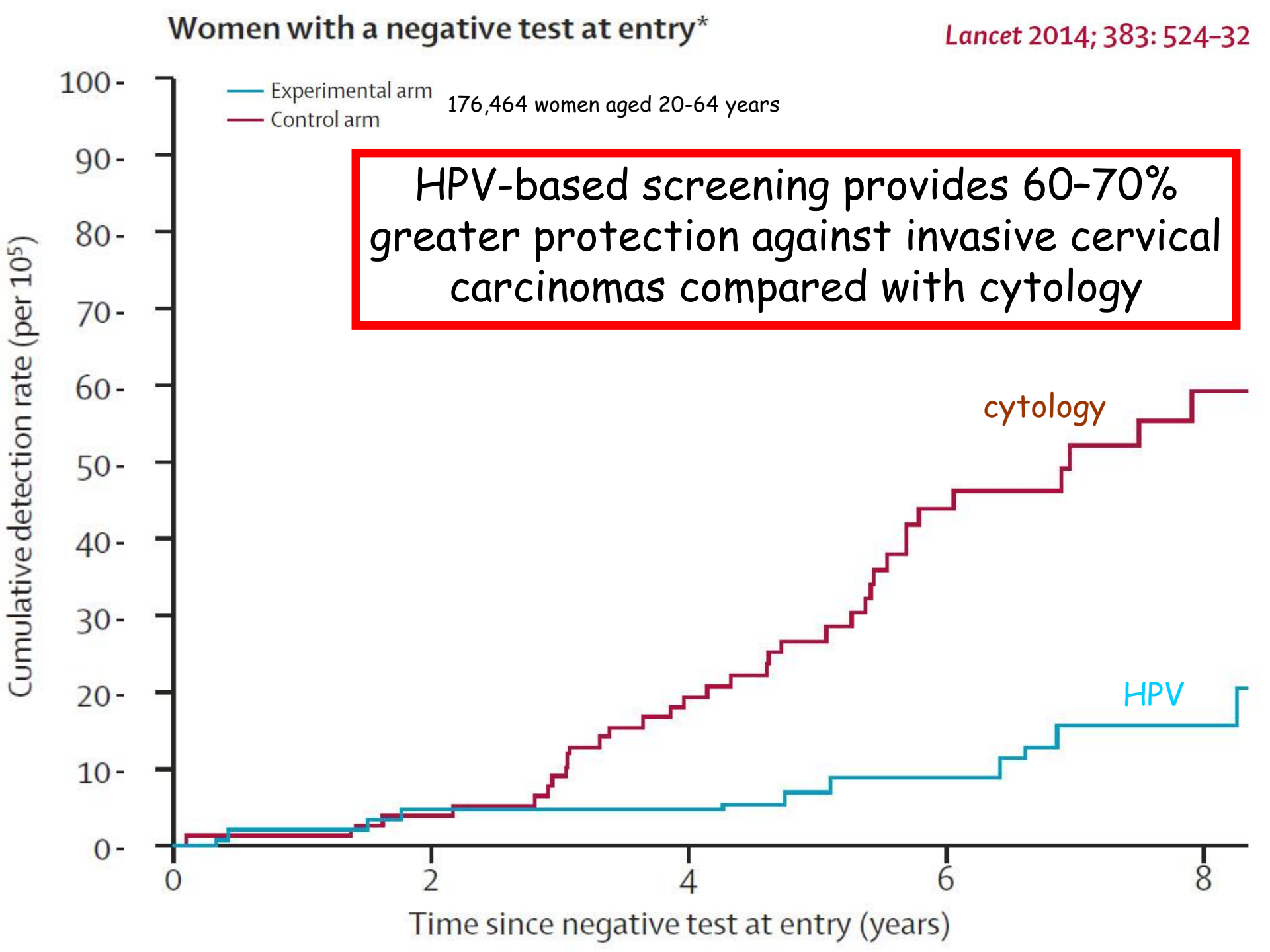
association between persistent HPV infection and cervical carcinoma is very strong, consistent, specific, and universal
(>15 times stronger than that between cigarette smoking and lung cancer)

cervical cancer only exceptionally develops in the absence of the persistent presence of HPV DNA

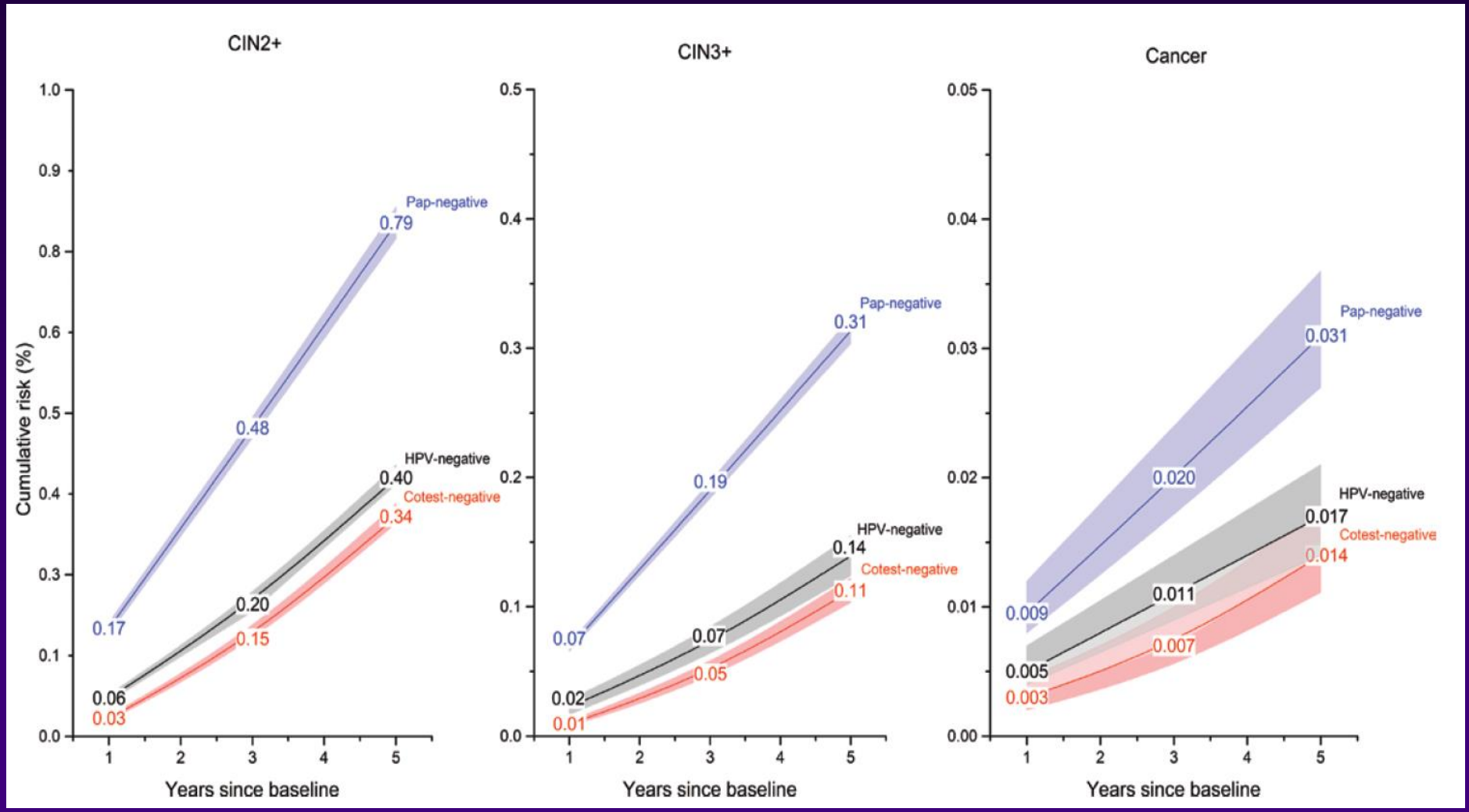
Global evaluation of the sensitivity (fraction of histology confirmed CIN 2+ detected by the test) of HPV tests as compared to cytology in studies in Europe and North America



Cuzick J et al. Int J Cancer 2006; 119: 1095-1101


Women with a negative test at entry*
Lancet 2014; 383: 524–32
Experimental arm
Control arm
176,464 women aged 20-64 years
HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas compared with cytology
cytology
HPV
Cumulative detection rate (per 10⁵)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
Time since negative test at entry (years)

Cumulative risk of CIN+2, CIN3+ and cervical cancer among 1,011,092 women aged 30 to 64 years at Kaiser Permanente Northern California by enrollment Pap and HPV test result; 2003 to 2012

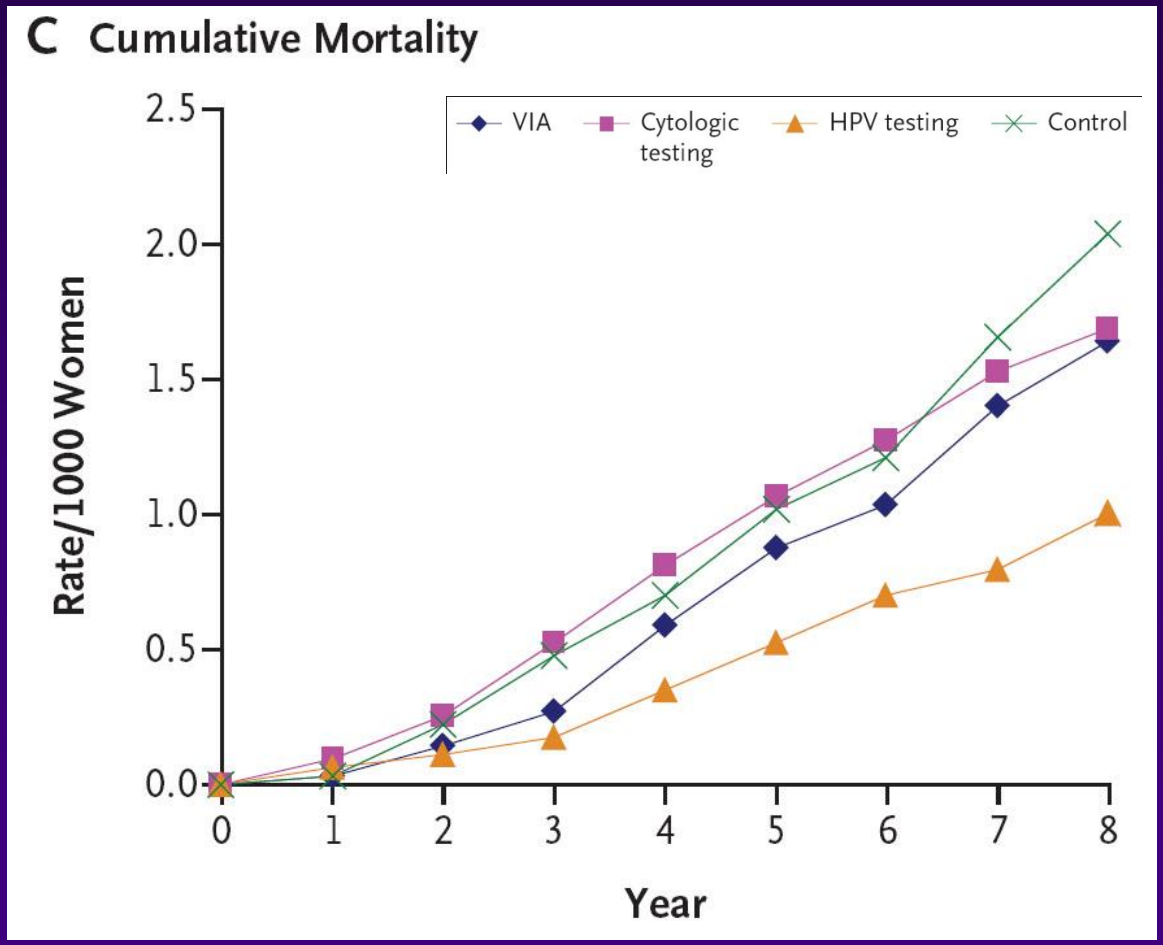


Gage JC et al. J Natl Cancer Inst 2014;106: dju153.

N Engl J Med 2009; 360: 1385-94

HPV Screening for Cervical Cancer in Rural India

Rengaswamy Sankaranarayanan, M.D., Bhagwan M. Nene, M.D., F.R.C.P., Surendra S. Shastri, M.D., Kasturi Jayant, M.Sc., Richard Muwonge, Ph.D., Atul M. Budukh, Ph.D., Sanjay Hingmire, B.Sc., Sylla G. Malvi, M.Sc., Ph.D., Ranjit Thorat, B.Sc., Ashok Kothari, M.D., Roshan Chinoy, M.D., Rohini Kelkar, M.D., Shubhada Kane, M.D., Sangeetha Desai, M.D., Vijay R. Keskar, M.S., Raghevendra Rajeshwarkar, M.D., Nandkumar Panse, B.Com., and Ketayun A. Dinshaw, M.D., F.R.C.R.

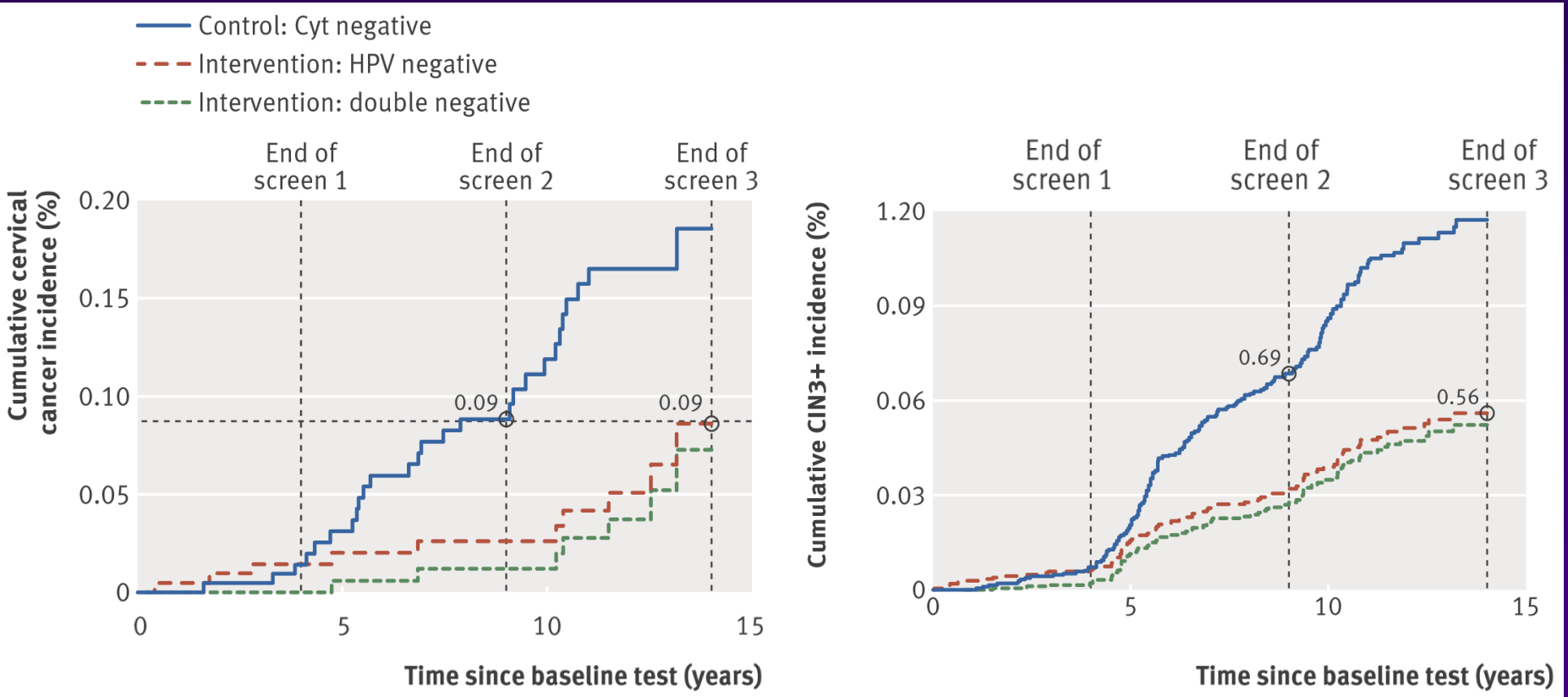


Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands

BMJ 2016;355:i4924

Maaike G Dijkstra,[1,2] Marjolein van Zummeren,[1] Lawrence Rozendaal,[1] Folkert J van Kemenade,[3] Theo J M Helmerhorst,[4] Peter J F Snijders,[1] Chris J L M Meijer,[1] Johannes Berkhof[5]

Cumulative incidence of cervical cancer and CIN3+ per trial group and baseline screening result, after up to three screening rounds



HPV-based primary cervical cancer screening

PRO:

- more sensitive than cytology to detect CIN2+, CIN3+ and cervical cancer
- more accurate and less variable than cytology
- risk of CIN2+ in women who are HPV negative is substantially lower than in women who are cytologically negative = extension of screening intervals possible and safe
- possibility of self-sampling testing

CON:

- reduced specificity of HPV DNA testing requires appropriate triage

Cervical cancer screening

HPV-testing and cytology (co-testing)

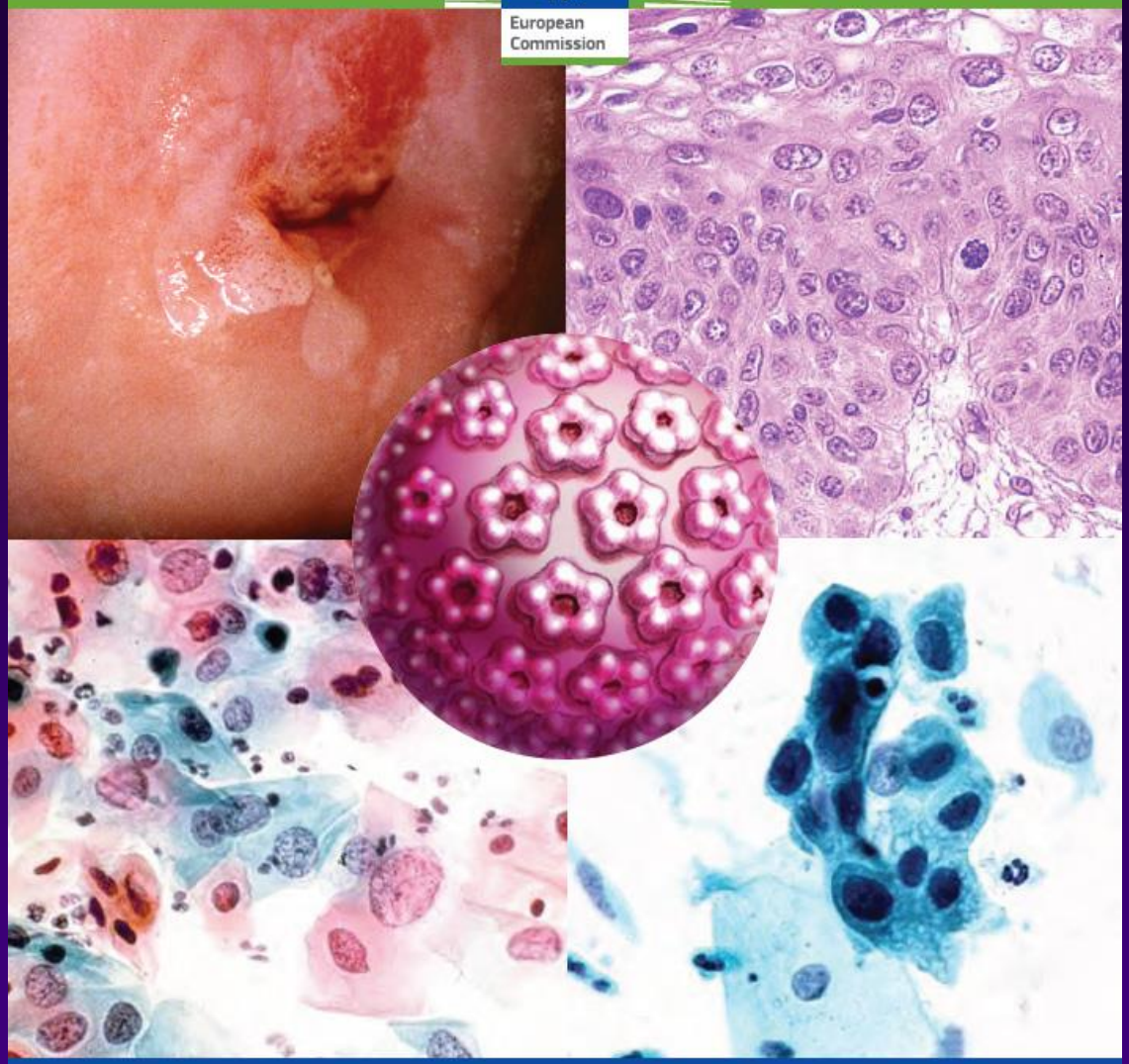
HPV-testing or cytology

Triage of HPV screen-positives

partial genotyping (HPV-16 and HPV-18)

cytology

European Union, 2015



European guidelines for quality assurance in cervical cancer screening

Second edition - Supplements

Papillomavirus Research 2015; doi:10.1016/j.pvr.2015.06.006.

European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination

Lawrence von Karsa [a,*], Marc Arbyn [b], Hugo De Vuyst [c], Joakim Dillner [d], Lena Dillner [e], Silvia Franceschi [f], Julietta Patnick [g], Guglielmo Ronco [h], Nereo Segnan [h], Eero Suonio [a], Sven Törnberg [i], Ahti Anttila [j]

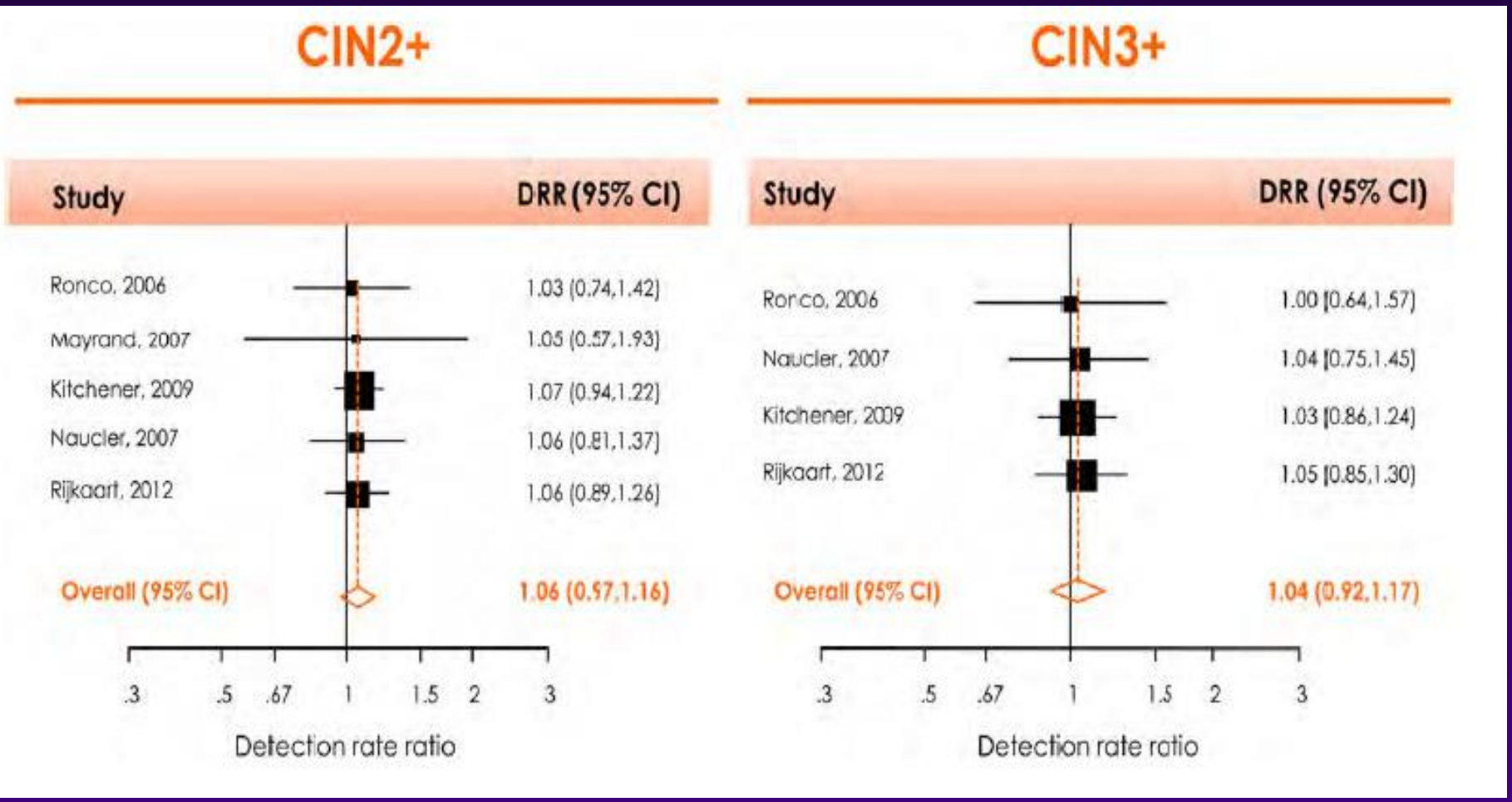
General recommendations

primary HPV testing can be used only in a population-based program for cervical cancer screening

HPV testing outside population-based programs is not recommended

only one primary screening test (either cytology or testing for oncogenic HPV) should be used at any given age in cervical cancer screening in Europe

Relative sensitivity of HPV primary testing in combination with cytology versus HPV primary testing alone



2015 European guidelines for quality assurance in cervical cancer screening

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Cervical Cancer

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

JAMA 2018;320(7):674-686

USPSTF recommends screening for cervical cancer:

every 3 years with cervical cytology alone in women aged 21 to 29 years (A recommendation)

screening every 3 years with cervical cytology alone, every 5 years with hrHPV testing alone, every 5 years with hrHPV testing in combination with cytology (co-testing) in women aged 30 to 65 years (A recommendation)

against screening for cervical cancer in women younger than 21 years (D recommendation)

HPV !!!

HPV test ?

Detection of HPV infection

Direct detection (detection of current infection)

- light microscopy (koilocytes)
- electron microscopy (viral particles)
- detection of viral proteins
- detection of viral DNA
- detection of viral mRNA

Detection of past and/or current infection

- detection of anti-HPV antibodies (measurement of cumulative exposure)

Commercially available alpha-HPV molecular tests

- periodical inventories -

2010

Poljak M, Kocjan BJ. Commercially available assays for multiplex detection of alpha human papillomaviruses. Exp Rev Anti Infect Ther 2010; 8: 1139-62.

2012

Poljak M, Cuzick J, Kocjan BJ, Iftner T, Dillner J, Arbyn M. Nucleic acid tests for the detection of alpha human papillomaviruses. Vaccine 2012; Suppl 30: F100-F106.

2015

Poljak M, Kocjan BJ, Oštrbenk A, Seme K. Commercially available molecular tests for human papillomaviruses (HPV): 2015 update. J Clin Virol 2016; 76: (Suppl 1): S3-S13.

2010 70 commercial HPV assays on the market

2012 125 commercial HPV assays (and 84 variants) on the market

2015 193 commercial HPV assays (and 127 variants) on the market

2017 246 commercial HPV assays (and 214 variants) on the market

- only 30.1% of HPV tests with published evaluation (analytical and/or clinical)
- "test A versus test B" approach with no reference standard
- ad hoc collections of heterogeneous clinical samples without follow-up

BUFFALO BILL'S WILD WEST

AND CONGRESS OF ROUGH RIDERS OF THE WORLD.

COL. W. F. CODY
BUFFALO BILL
WILL APPEAR
AT EVERY PERFORMANCE

A COMPANY OF WILD WEST COWBOYS, THE REAL ROUGH RIDERS OF THE WORLD WHOSE DARING EXPLOITS HAVE MADE THEIR VERY NAMES SYNONYMOUS WITH DEEDS OF BRAVERY.

HPV !!!

HPV test ?

HPV tests for agreed indications for HPV testing in current clinical practice

HPV tests for epidemiological and vaccine-related studies

HPV tests for different research purposes

*****

two most important parameters which define the purpose of the HPV test

(i) set of targeted HPV types

(ii) level of analytical sensitivity

Ideal HPV Test

for major agreed indications for HPV testing in current clinical practice

HPV test should:

- detect all HPV infections that are associated with, or will develop into high-grade CIN
- differentiate them completely from transient HPV infections

based on prediction of cervical cancer and NOT the presence of virus

Broad genotype coverage

High analytical sensitivity

High analytical specificity

HPV Test

for major agreed indications for HPV testing in current clinical practice

Broad genotype coverage	BALANCED = ARTIFICIALLY REDUCED
High analytical sensitivity	BALANCED = ARTIFICIALLY REDUCED
High analytical specificity	NECESSARY

HPV Test

for major agreed indications for HPV testing in current clinical practice

Broad genotype coverage	BALANCED = ARTIFICIALLY REDUCED
High analytical sensitivity	BALANCED = ARTIFICIALLY REDUCED
High analytical specificity	NECESSARY

High clinical sensitivity !!!!

High clinical specificity !!!!

CIN 2+

Ideal HPV Test

for major agreed indications for HPV testing in current clinical practice

optimal balance between clinical sensitivity and clinical specificity for CIN2+

aim to minimize redundant/excessive follow-up procedures for hr-HPV positive women with transient hr-HPV infections and/or without cervical lesions

*****

HPV assay with very high analytical sensitivity yields a large number of clinically insignificant positive results resulting in unnecessary follow-up, diagnostics procedures and treatment of healthy women

Which high-risk HPV assays fulfil the criteria for use in primary cervical cancer screening ?

Regulatory approvals

US Food and Drug Administration (FDA) approval

Co-testing (every 5 years, >=30 years)

Hybrid Capture 2 (hc2) HPV DNA Test (Qiagen)

Cervista HPV HR Test + Cervista HPV 16/18 Test (Hologic)

APTIMA HPV Assay + APTIMA HPV 16 18/45 genotype assay (Hologic)

cobas 4800 HPV Test (Roche)

BD Onclarity HPV assay (Becton Dickinson)

HPV testing only (every 3 years, >=30 years)

cobas 4800 HPV Test (Roche)

BD Onclarity HPV assay (Becton Dickinson)

Which high-risk HPV assays fulfil the criteria for use in primary cervical cancer screening ?

Regulatory approvals

US Food and Drug Administration (FDA) approval

Academic validations

- International guidelines (Meijer's criteria)
- Valgent 1-4
- Academic multi-test comparisons (PREDICTORS 3)

Which high-risk HPV assays fulfil the criteria for use in primary cervical cancer screening ?

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US Food and Drug Administration (FDA) approval

Academic validations

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- Academic multi-test comparisons (PREDICTORS 3)

Int. J. Cancer: **124,** 516–520 (2009)

FAST TRACK

Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older

Chris J.L.M. Meijer[1]*, Johannes Berkhof[2], Philip E. Castle[3], Albertus T. Hesselink[1], Eduardo L. Franco[4], Guglielmo Ronco[5], Marc Arbyn[6,7], F. Xavier Bosch[8], Jack Cuzick[9], Joakim Dillner[10], Daniëlle A.M. Heideman[1] and Peter J.F. Snijders[1]

[1]*Department of Pathology, VU University Medical Center, 1007 MB Amsterdam, The Netherlands*
[2]*Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, 1007 MB Amsterdam, The Netherlands*
[3]*Department of Cancer Epidemiology and Genetics, National Institute of Health, Washington, DC*
[4]*Division of Cancer Epidemiology, McGill University, Montreal, Canada*
[5]*Unit of Cancer Epidemiology, Centro per la prevenzione Oncologica, Turin, Italy*
[6]*Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium*
[7]*ECCG (European Cooperation on Development and Implementation of Cancer Screening and Prevention Guidelines), IARC, Lyon, France*
[8]*Servei d'epidemiologia, Institut Catala d'Oncologia (ICO), Hospitalet del llobregat, Barcelona, Spain*
[9]*Queen Mary's School of Medicine and Dentistry and Cancer Research UK, London, United Kingdom*
[10]*Department of Medical Microbiology University Hospital, Lund University, Malmö, Sweden*

relative clinical accuracy compared to either of two HPV tests which demonstrated lower cumulative incidence of cervical cancer 5 years after a negative HPV test than 3 years after a normal cytology in four large European randomized trials

Int. J. Cancer: **124,** 516–520 (2009)

FAST TRACK

Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older

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Requirements for HPV tests in primary cervical screening

1. A clinical sensitivity for CIN2+ not less than 90% of the clinical sensitivity of the hc2 in women of at least 30 years.

2. A clinical specificity for CIN2+ not less than 98% of the clinical specificity of the hc2 in women of at least 30 years of age.

3. Intra-laboratory reproducibility and inter-laboratory agreement with a lower confidence bound not less than 87%.

Which high-risk HPV assays fulfil the criteria for use in primary cervical cancer screening ?

Regulatory approvals

US Food and Drug Administration (FDA) approval

Academic validations

- International guidelines (Meijer's criteria)
- Valgent 1-4
- Academic multi-test comparisons (PREDICTORS 3)

VALGENT 1

5 HPV assays - samples derived from a Belgian biobank

VALGENT 2

6 HPV assays - samples derived from Scottish HPV archive

VALGENT 3

13 HPV assays – samples derived from Slovenian national cohort

VALGENT 4

11 HPV assays – samples from Copenhagen, Denmark

Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening?

Clin Microbiol Infect 2015;21:817-26

M. Arbyn[1], P. J. F. Snijders[2], C. J. L. M. Meijer[2], J. Berkhof[3], K. Cuschieri[4], B. J. Kocjan[5] and M. Poljak[5]

1) *Unit of Cancer Epidemiology and Belgian Cancer Centre, Scientific Institute of Public Health, Brussels, Belgium,* 2) *Department of Pathology,* 3) *Department of Clinical Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, The Netherlands,* 4) *Scottish HPV Reference Laboratory, Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK and* 5) *Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*

UPDATE OF THE LIST OF HPV ASSAYS THAT FULFILL REQUIREMENTS FOR PRIMARY CERVICAL CANCER SCREENING

M. Arbyn[1], M. Poljak[2], C.J.L.M. Meijer[3], P.J.F. Snijders[3], J. Berkhof[4], K. Cuschieri[5], I. Heard[6], J. Bogers[7,8], C. Depuydt[7], D. Vanden Broeck[7,8], I. Benoy[7,8], J. Bonde[9], T. Gheit[10], M. Tommasino[10], M. Pawlita[11], I. Iftner[12], P. Sasieni[13], D. Geraets[14], W. Quint[14]

submitted

Hybrid Capture 2 (hc2) HPV DNA Test (Qiagen) Status: March 2019

EIA kit HPV GP HR (Labo Bio-medical Products)

cobas 4800 HPV Test (Roche)

APTIMA HPV Assay (Hologic)

Cervista HPV HR Test (Hologic)

RealTime High Risk HPV test (Abbott)

PapilloCheck HPV-screening test (Greiner Bio-One)

Real-time quantitative PCR (qPCR) assay targeting the E6 and E7 genes (Riatol - Belgian private lab)

HPV-Risk assay (Self-Screen)

BD Onclarity HPV Assay (Becton Dickinson)

LMNX genotyping kit HPV GP HR (Labo Bio-medical Products) - previous digene HPV Genotyping LQ Test

Anyplex II HPV HR (Seegene)

Xpert HPV (Cepheid)

EUROArray HPV Test (EuroImmun)

Linear Array HPV Genotyping Test (Roche) - restricted to 13 hrHPV types

- 246+ commercial HPV assays (and 214+ variants) on the market
- 2 + 13 HPV assays fulfil cross-sectional criteria for primary screening
- 2 + 4 HPV assays have at least 36+ months longitudinal data

non-validated HPV tests should not be used in clinical management

HPV test ?


KALKAN
KG 40 000
40YTL
LEVREK
KG 14000
14 YTL
LEVREK
25YTL
PALAMUT
CUPRA
KG 14000
14 YTL
ALABALIK
TANE 2500
2 50 YTL
KARIDES
KG30 000
30 YTL