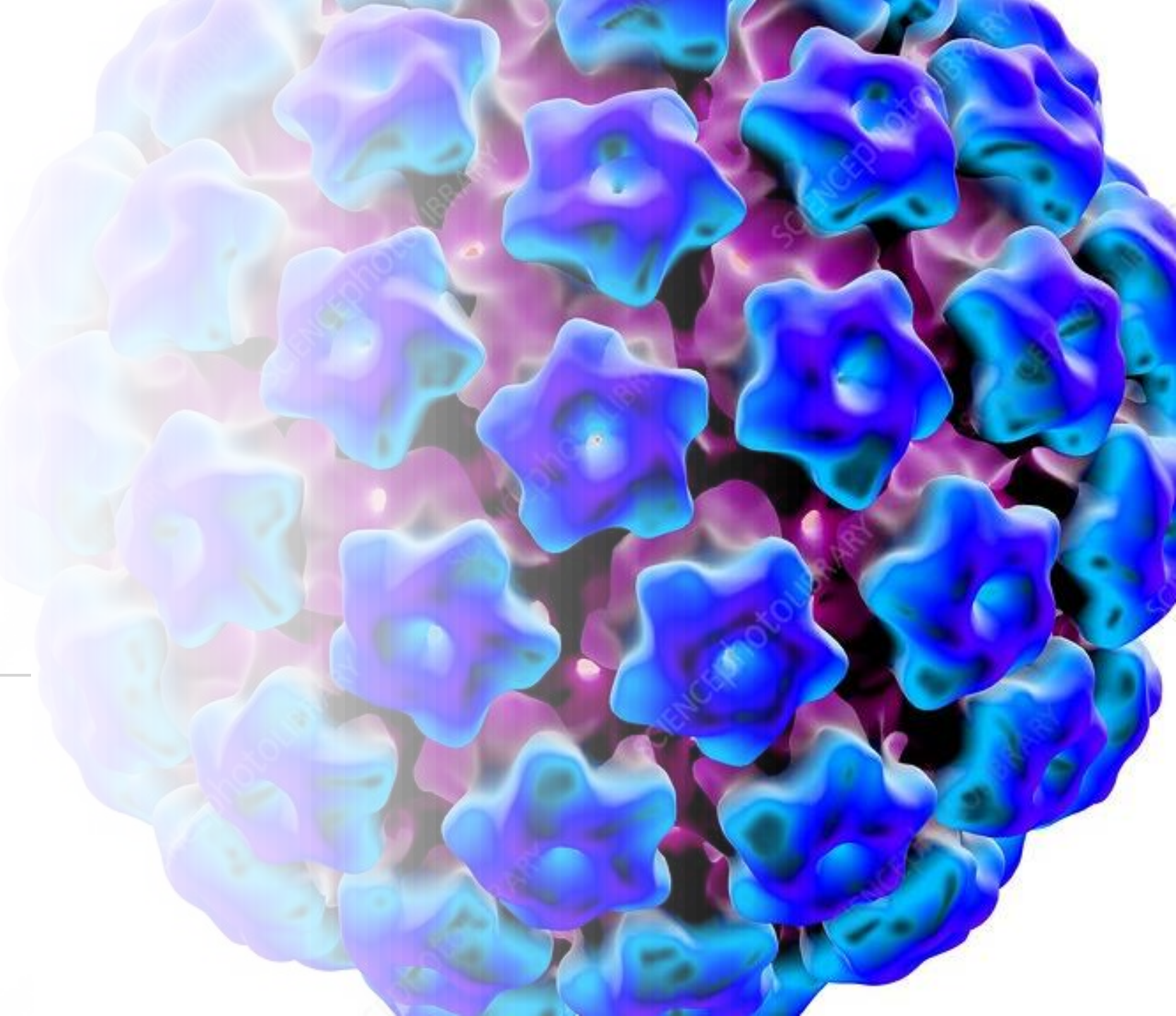
Klinische implementatie van primaire HPV screening

12/11/2024

Kobe Dewilde




Schoenmaker
blijf bij je leest

PCR EXPLAINED

FOR DUMMIES

1. DENATURATION

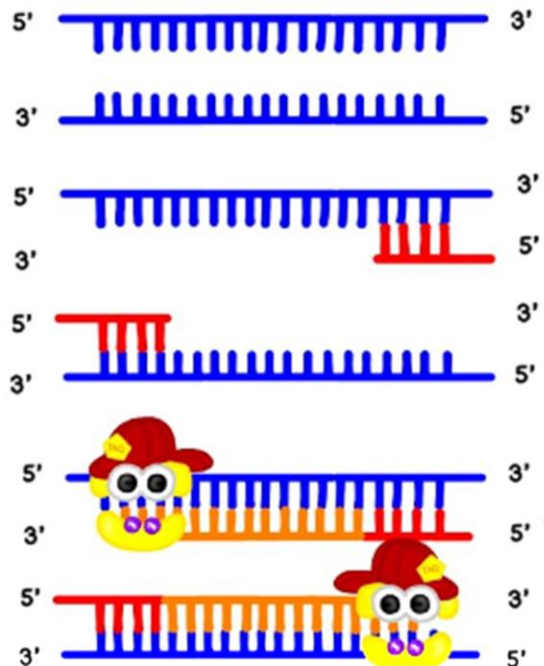
~95°C

2. ANNEALING

~55°C

3. EXTENSION

~72 °C



DNA STRANDS SEPARATE

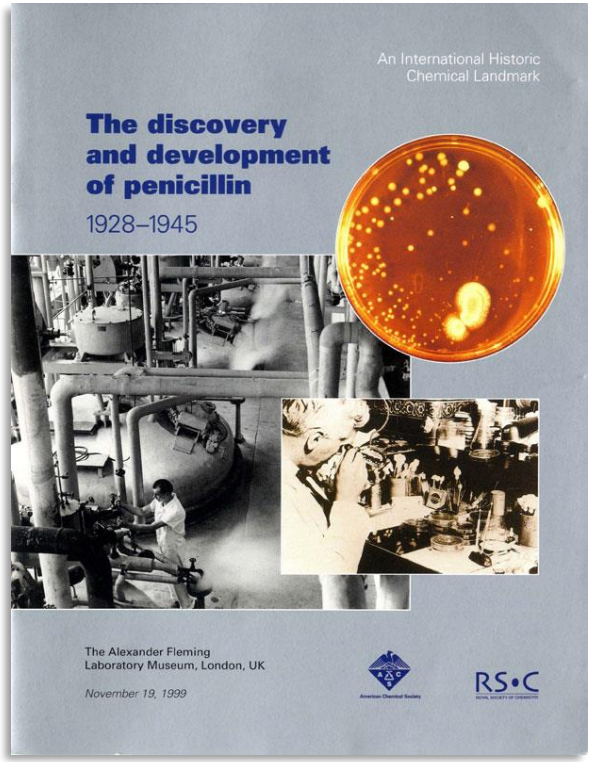
PRIMERS ADHERE TO DNA STRANDS

TAQ POLYMERASE BUILDS COMPLEMENTARY STRAND

Klinische insteek

- **HPV**
- **Cervix Screening**
- **Huidige Screening**
- **Waarom HPV**
- **Nieuwe screening**

1928



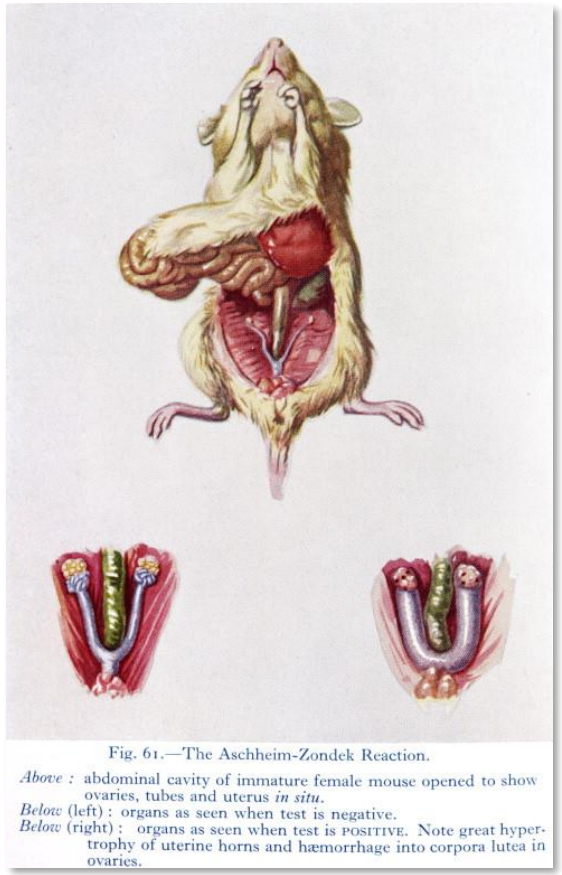
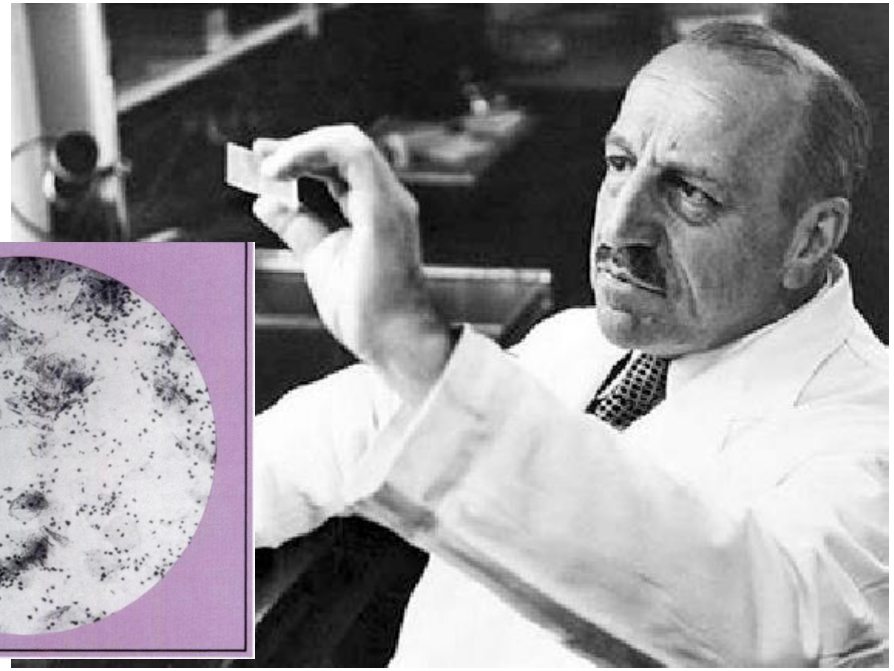


Fig. 61.—The Aschheim-Zondek Reaction.

Above : abdominal cavity of immature female mouse opened to show ovaries, tubes and uterus *in situ*.
Below (left) : organs as seen when test is negative.
Below (right) : organs as seen when test is POSITIVE. Note great hypertrophy of uterine horns and hæmorrhage into corpora lutea in ovaries.



This paper was originally presented at the Third Race Betterment Conference, Battle Creek, Michigan, January 2-6, 1928, and published in the Proceedings of the Conference the same year.

American Journal of Obstetrics and Gynecology

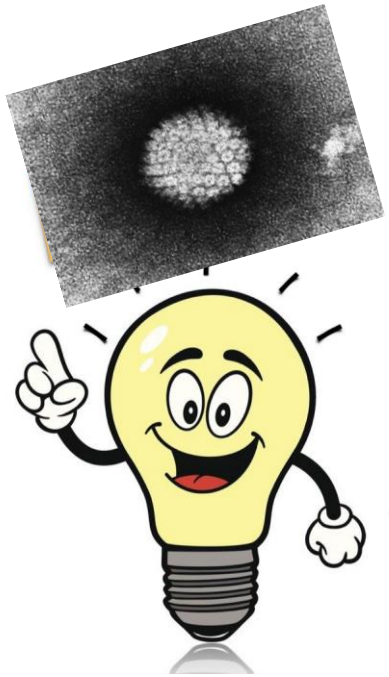
VOL. 42 AUGUST, 1941 No. 2

Original Communications

THE DIAGNOSTIC VALUE OF VAGINAL SMEARS IN CARCINOMA OF THE UTERUS*

GEORGE N. PAPANICOLAOU, M.D., PH.D., AND HERBERT F. TRAUT, M.D.,
NEW YORK, N. Y.

(From the Departments of Anatomy and of Gynecology and Obstetrics of the Cornell University Medical College and the New York Hospital)



Cancer Res. 1976 Feb;36(2 pt 2):794.

Condylomata acuminata and human genital cancer

H zur Hausen

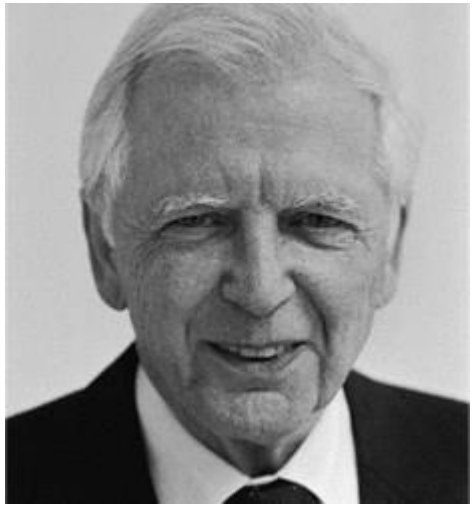


Fig. 1.9 Phylogeny of the alpha human papillomavirus (HPV) types, with species groups and IARC classifications of the branch that contains carcinogenic types

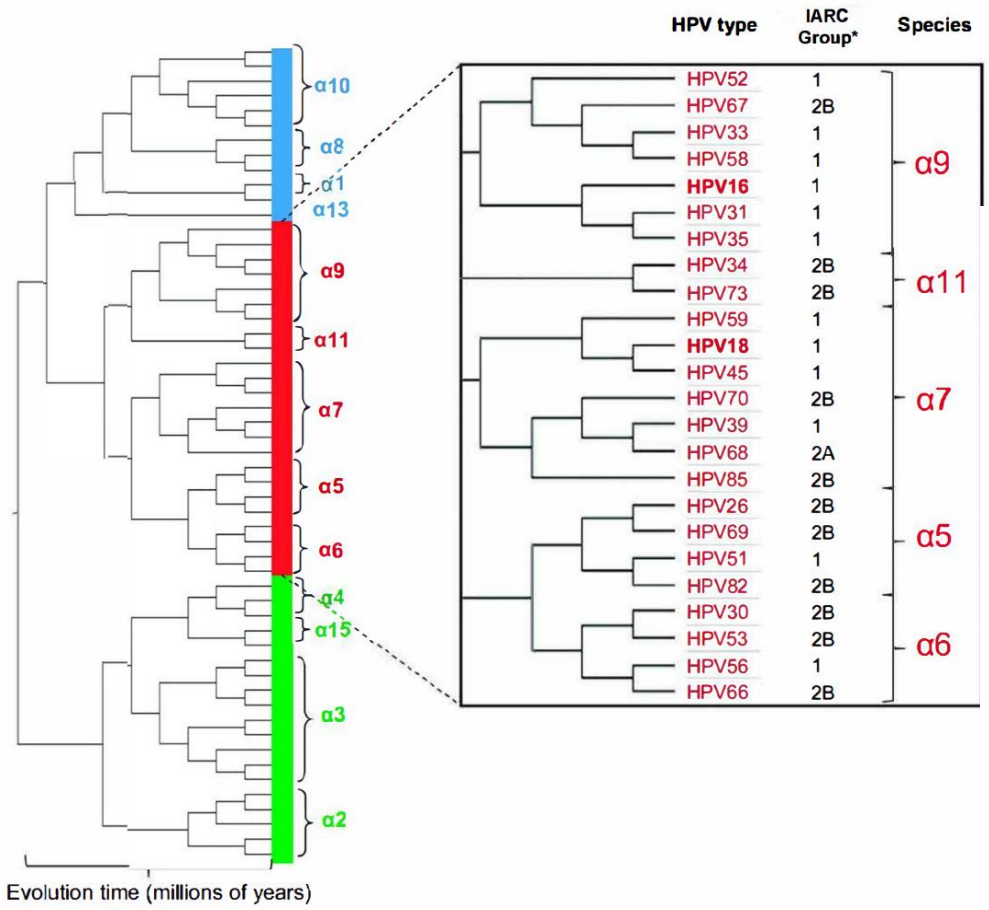


Fig. 1.10 Relative importance of the carcinogenic human papillomavirus (HPV) types

HPV type	HPV species	IARC Group[a]	% HPV type prevalence in cancer	% HPV type prevalence in normal	Odds ratio	% Attributable (etiological) fraction
HPV16	**α-9**	**Group 1**	**55.8**	**2.6**	**47.6**	**62.4**
HPV18	**α-7**	**Group 1**	**14.3**	**1**	**15.7**	**15.3**
HPV45	**α-7**	**Group 1**	**4.8**	**0.6**	**8.3**	**4.8**
HPV33	**α-9**	**Group 1**	**4**	**0.6**	**7.1**	**3.9**
HPV58	**α-9**	**Group 1**	**4**	**0.8**	**5.1**	**3.7**
HPV31	**α-9**	**Group 1**	**3.5**	**1**	**3.7**	**2.9**
HPV52	**α-9**	**Group 1**	**3.2**	**1**	**3.3**	**2.6**
HPV35	**α-9**	**Group 1**	**1.6**	**0.4**	**3.9**	**1.4**
HPV59	**α-7**	**Group 1**	**1.2**	**0.4**	**2.9**	**0.9**
HPV39	**α-7**	**Group 1**	**1.3**	**0.6**	**2.0**	**0.8**
HPV68	**α-7**	**Group 2A**	**0.6**	**0.4**	**1.5**	**0.2**
HPV51	**α-5**	**Group 1**	**1**	**0.9**	**1.2**	**0.2**
HPV56	**α-6**	**Group 1**	**0.8**	**0.6**	**1.3**	**0.2**
HPV73	α-11	Group 2B	0.5	0.3	1.8	0.2
HPV26	α-5	Group 2B	0.2	0.1	4.1	0.2
HPV30	α-6	Group 2B	0.2	0.1	2.6	0.1
HPV69	α-5	Group 2B	0.2	0.1	1.4	0.1
HPV67	α-9	Group 2B	0.3	0.2	1.2	< 0.1
HPV82	α-5	Group 2B	0.2	0.1	1.2	< 0.1
HPV34	α-11	Group 2B	0.1	0.1	1.0	Not attributable
HPV66	**α-6**	**Group 2B**	**0.3**	**0.6**	**0.4**	**Not attributable**
HPV70	α-7	Group 2B	0.2	0.8	0.3	Not attributable
HPV53	α-6	Group 2B	0.5	1.1	0.4	Not attributable

82,5%

14,5%

2,3%

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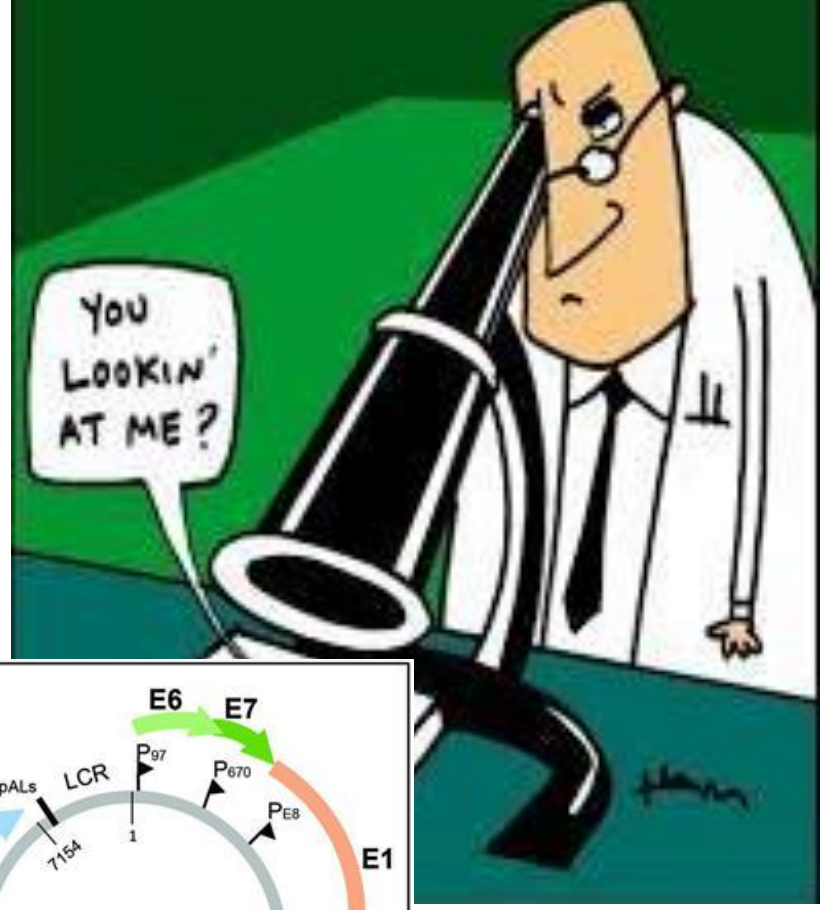
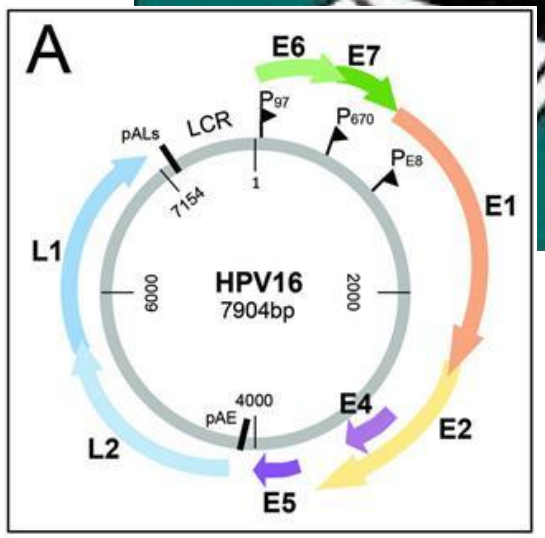




Function in viral lifecycle	Activities	Target factor
E1		
Replication of viral genome	DNA-binding activity, helicase activity, ATPase	RPA, topoisomerase, polymerase alpha-primase
E2		
Transcription of viral genes Replication of viral genome Maintenance of viral genome	Transactivation/transrepression, DNA-binding activity, DNA segregation in mitotic cell	Brd4, ChlR1
E6		
Reactivation of cellular replication mechanisms Proliferation, immortalization, inhibition of apoptosis Maintenance of viral genome	Interaction with various cellular proteins	p53, ADA3, p300/CBP, E6AP, SP1, c-Myc, NFX1-91, TERT, FAK, FADD, Caspase 8, BAX, BAK, IRF3, PDZ domain proteins
E7		
Reactivation of cellular replication mechanisms Proliferation, genomic instability, inhibition of apoptosis Maintenance of viral genome	Interaction with various cellular proteins	RB, p107, p130, HDAC, E2F6, p21, p27, CDK/cyclin, ATM, ATR, gamma-tubulin
E4		
Unknown	Destruction of keratin network, induction of G_2M arrest of cell cycle	Cytokeratin 8/18
E5		
Possibly involved in proliferation and/or inhibition of apoptosis	Affection of cellular signaling pathway	EGFR, PDGFR, V-ATPase, MHC1, TRAIL receptor, FAS receptor
L1		
Major capsid protein		
L2		
Minor capsid protein		

Graham, *Clin Sci (Lond)* (2017) 131 (17): 2201–2221.

Kajitani et al. Front. Microbiol., 24 April 2012 | https://doi.org/10.3389/fmicb.2012.00152

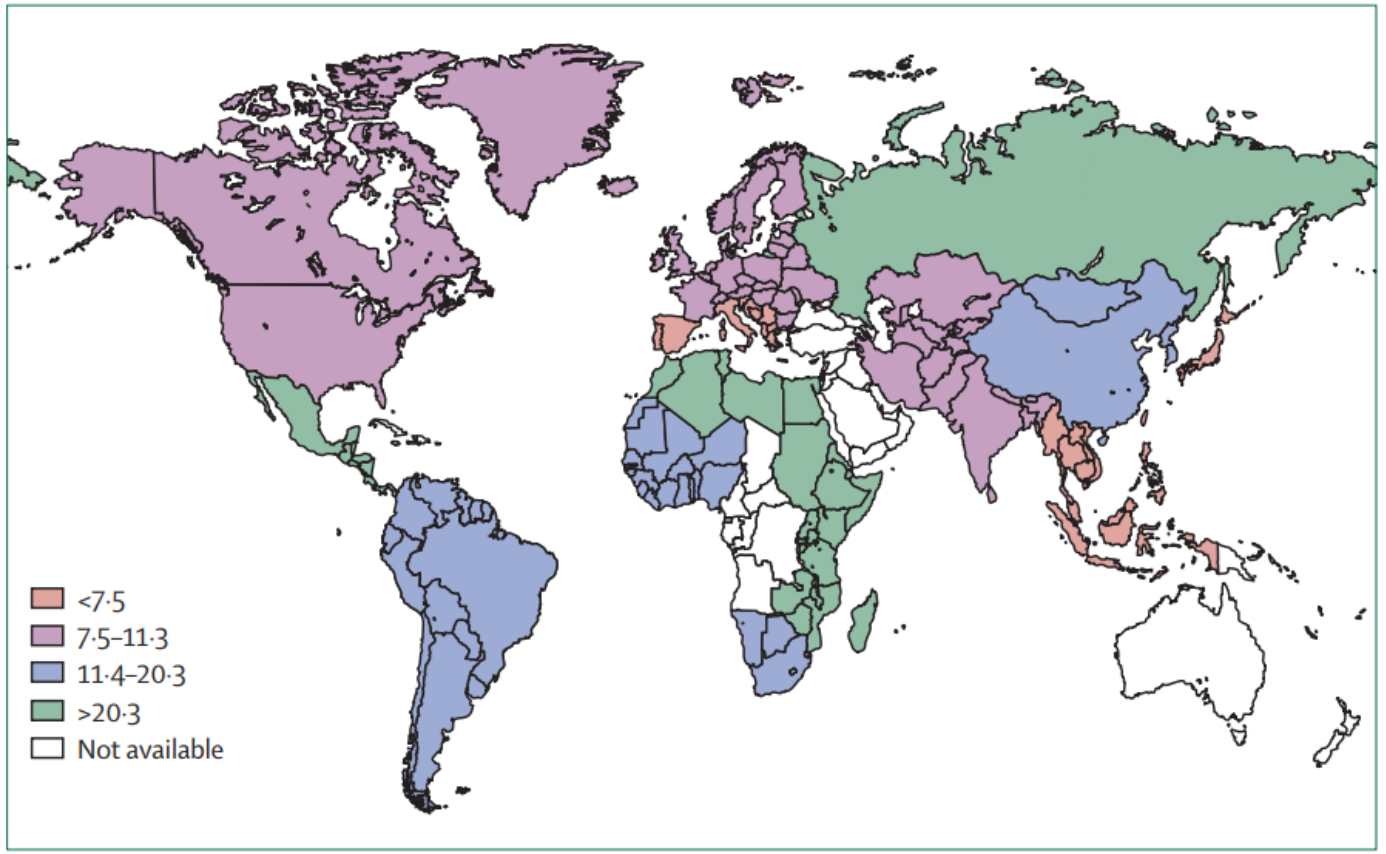


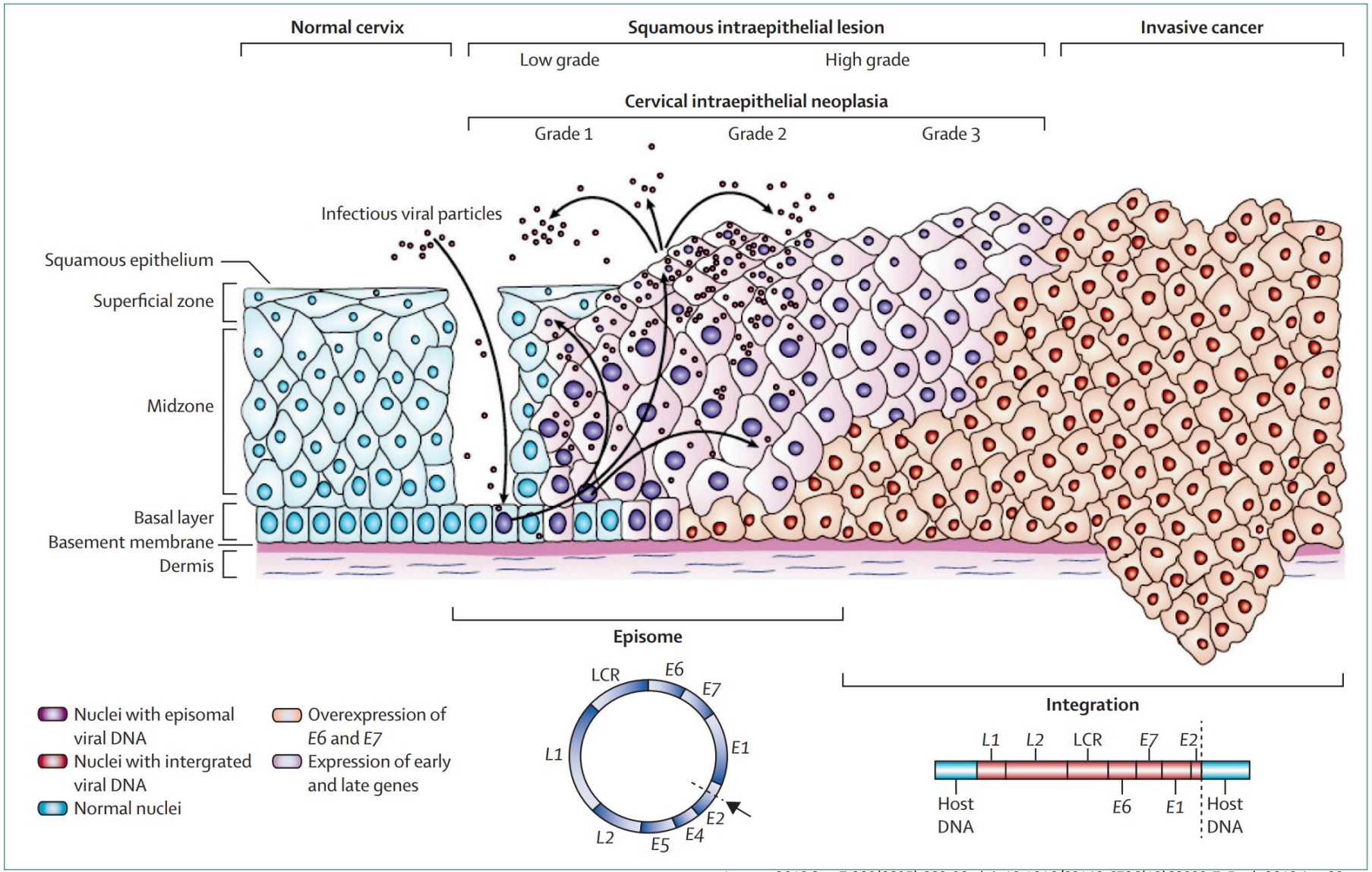
***Figure 1*: Estimated HPV DNA prevalence in the world regions**

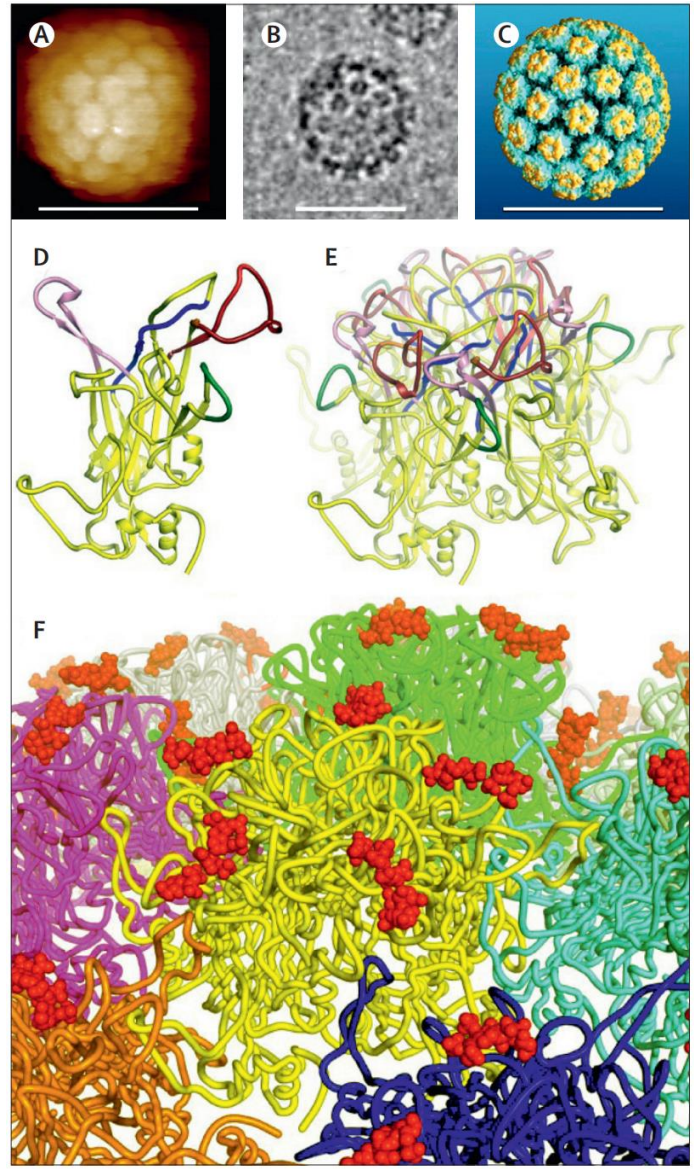
Estimates are based on a meta-analysis of 78 studies including 157 879 women with normal cytology. Colours represent the adjusted prevalence in the region and denote the quartile distribution of all the estimates.

de Sanjosé et al. Lancet Infect Dis 2007; 7: 453–59

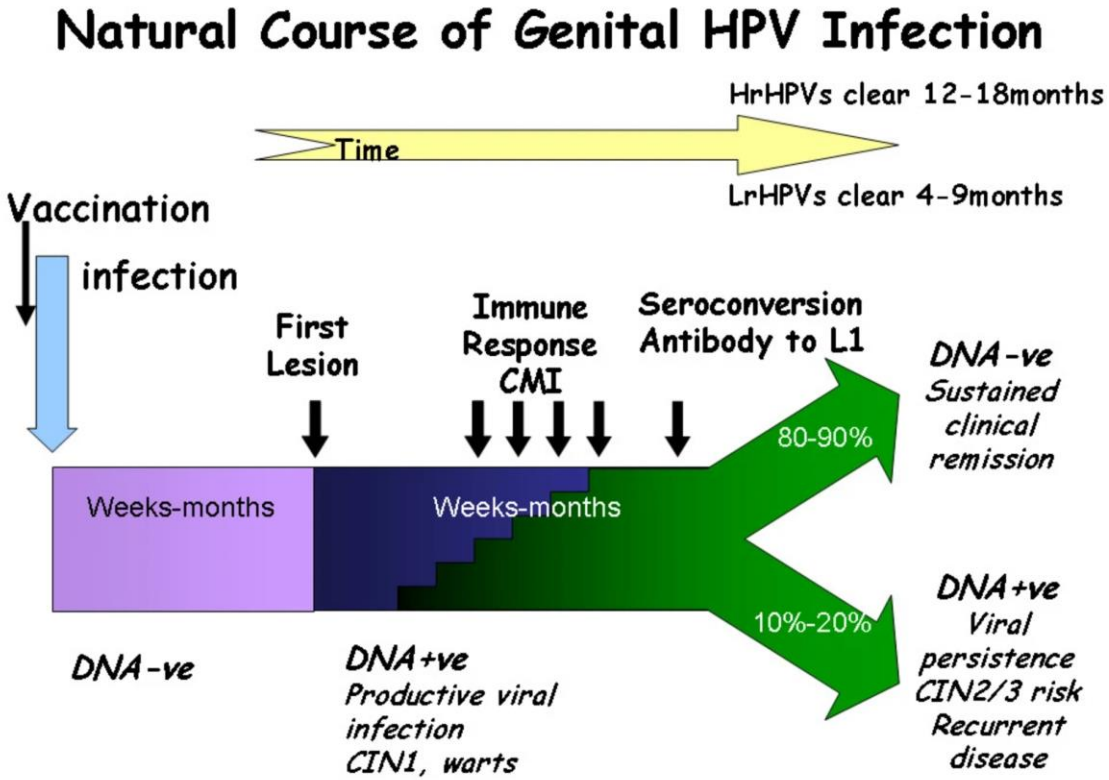
***Figure 4*: Ranking of the five most common HPV types among women with normal cytology within world regions and in the world**

Data are based on meta-analysis of 48 studies. Each estimate has been weighted by the number of women tested for each HPV type. Number of studies included in brackets



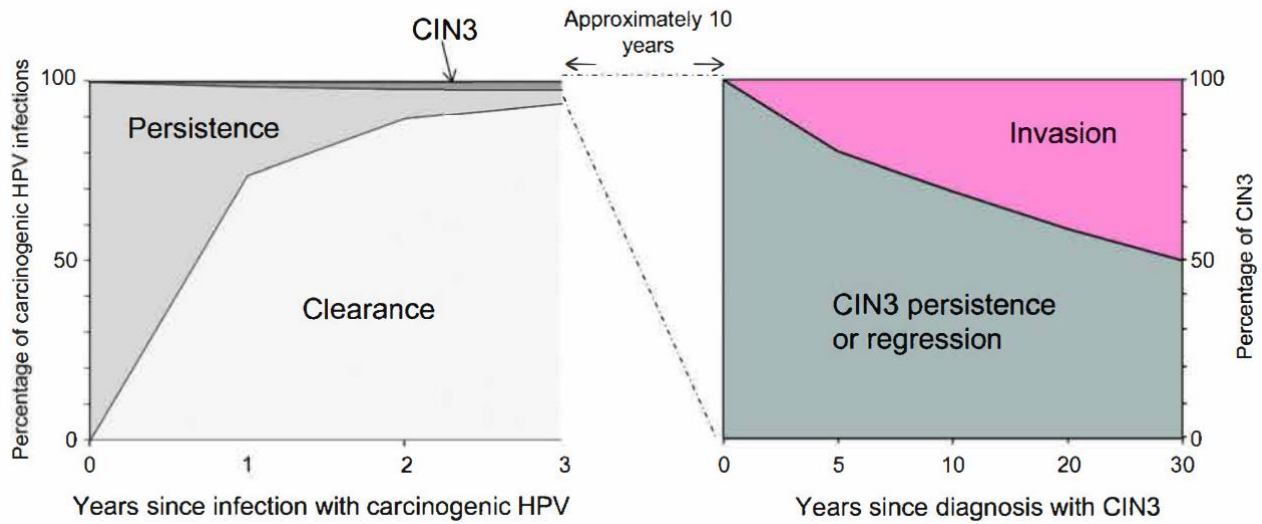


Lancet. 2013 Sep 7;382(9895):889-99. doi: 10.1016/S0140-6736(13)60022-7. Epub 2013 Apr 23.



Stanley, M. HPV - immune response to infection and vaccination. *Infect Agents Cancer* **5,** 19 (2010).

Fig. 1.14 Average clearance, persistence, and progression of carcinogenic human papillomavirus (HPV) infections



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CURRENT OPINION
Re-evaluation

The significance of cervical carcinoma in situ

G. H. GREEN, M.B., CH.B., F.R.C.O.G.
Auckland, New Zealand

After a decade of experience the evidence that cytology programs can eventually eliminate invasive cervical cancer remains doubtful. The one solid achievement of cytology in National Women's Hospital has been the revealing of invasive cancer at an earlier stage.

› Am J Obstet Gynecol. 1966 Apr 1;94(7):1009-22. doi: 10.1016/0002-9378(66)90041-x.

Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study

Margaret R E McCredie, Katrina J Sharples, Charlotte Paul, Judith Baranyai, Gabriele Medley, Ronald W Jones, David C G Skegg

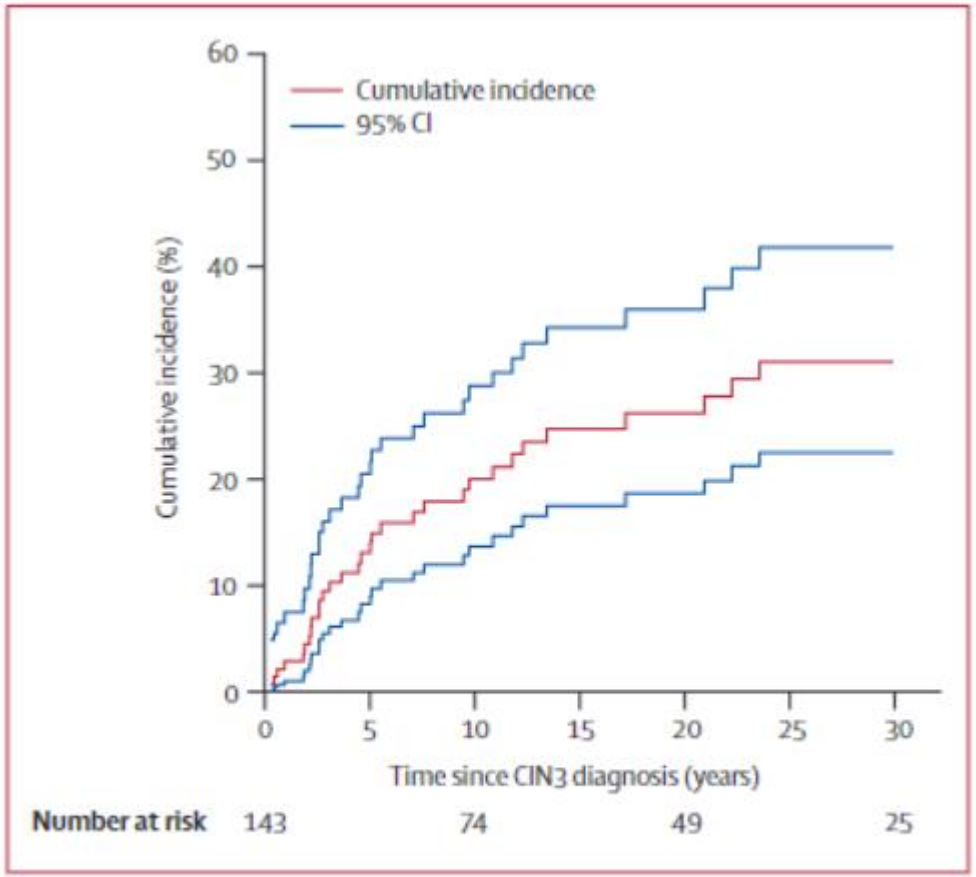


Figure 3: Cumulative incidence of cancer of the cervix or vaginal vault in women with minimum disturbance of the CIN3 lesion (no more than a punch or wedge biopsy)

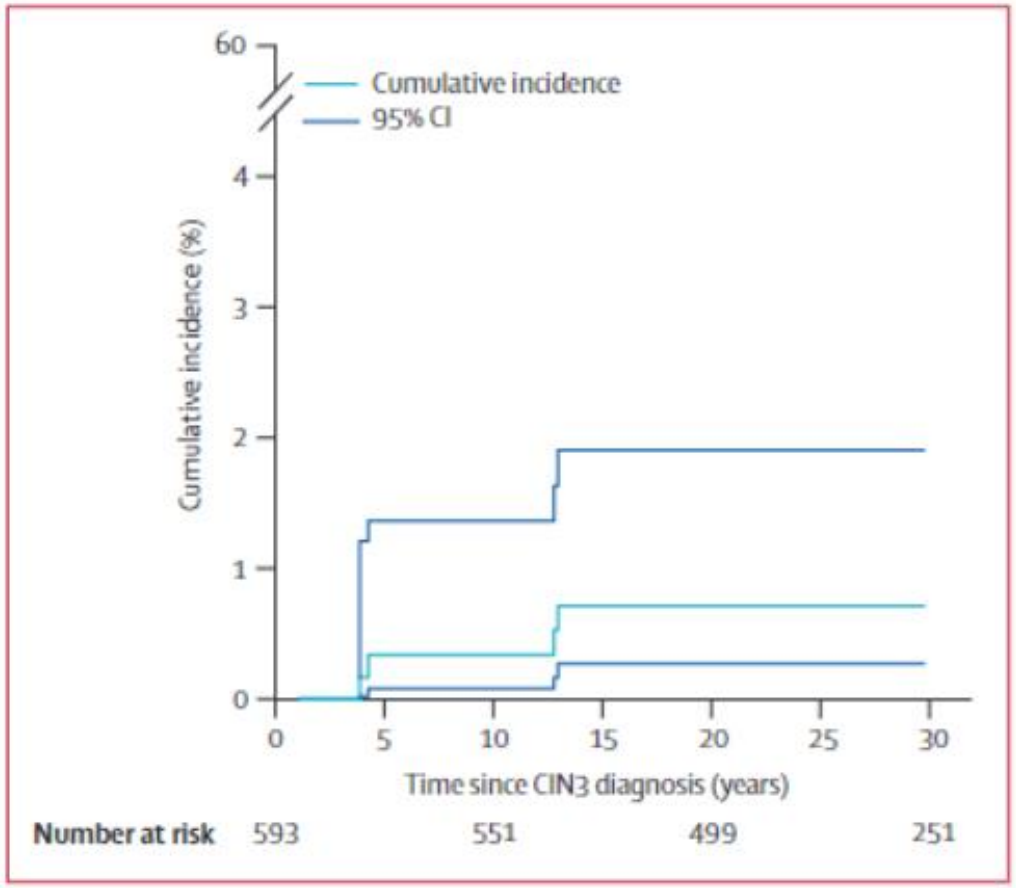
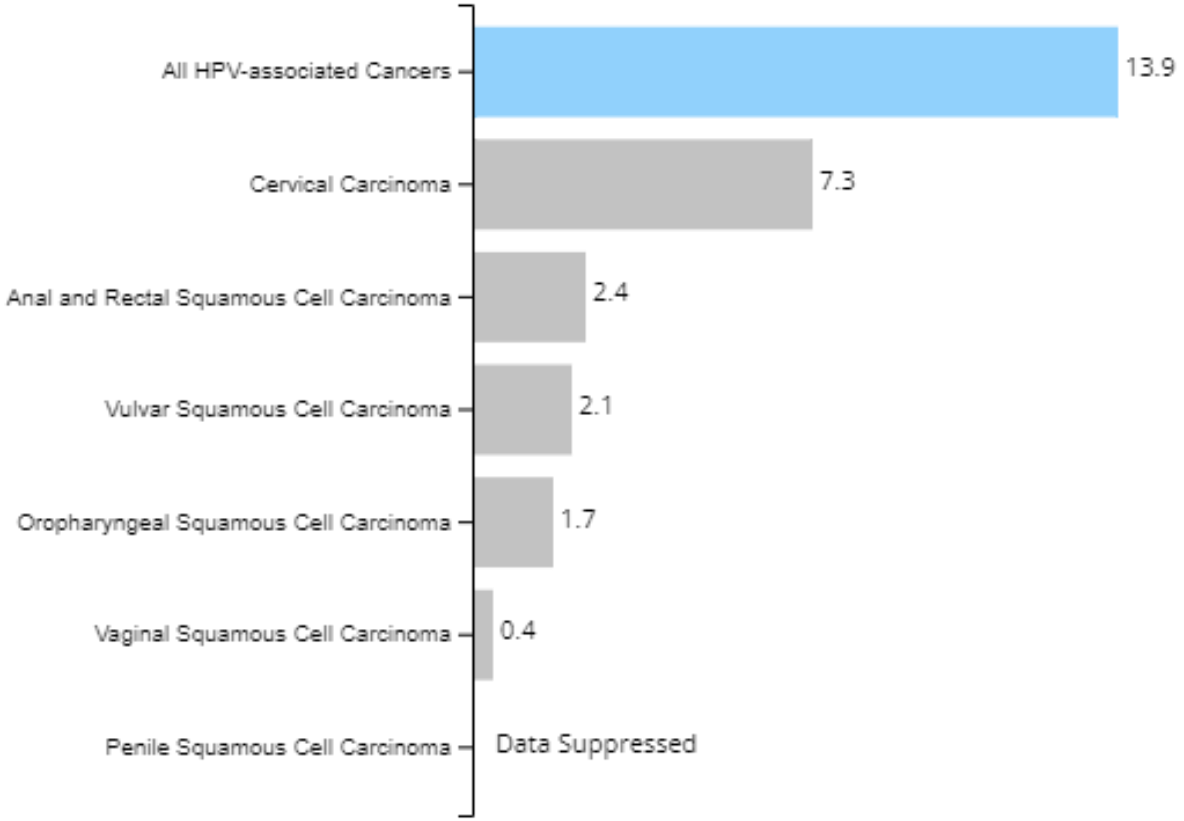


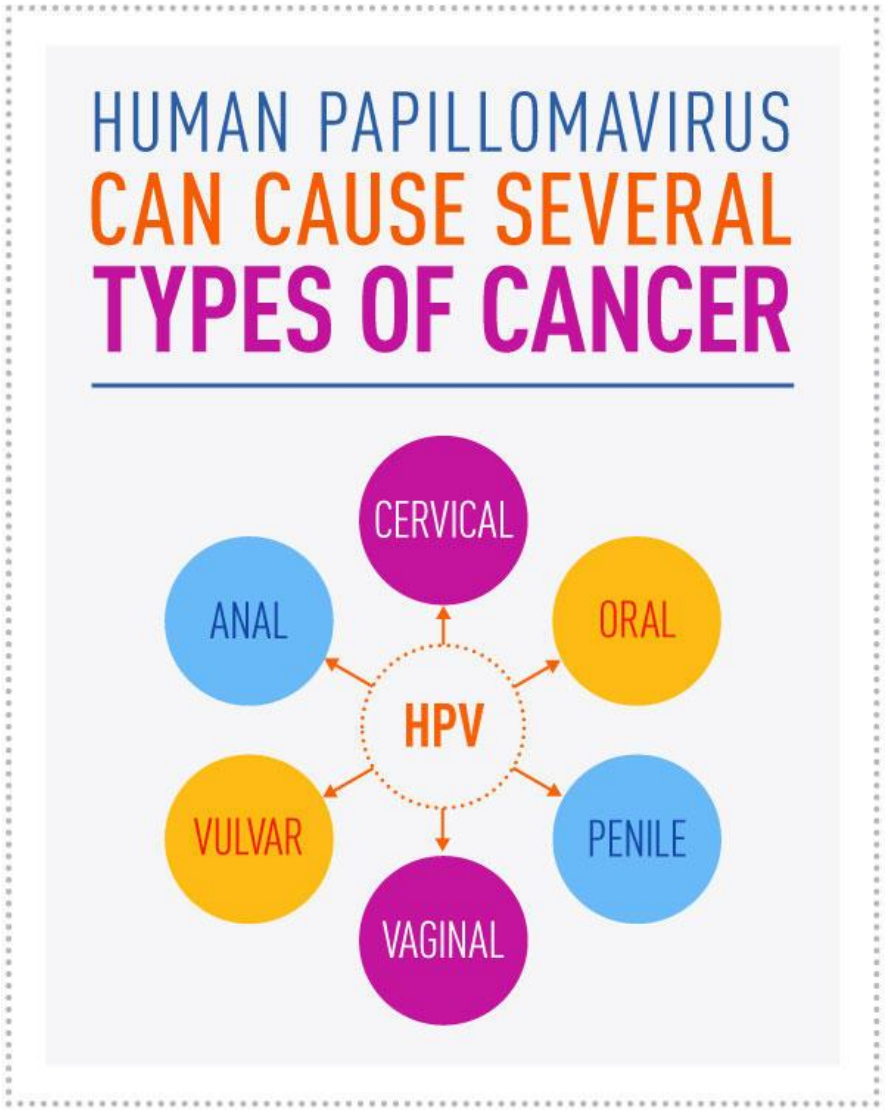
Figure 4: Cumulative incidence of cancer of the cervix or vaginal vault in women with initial treatment classified as adequate or probably adequate and conventional management thereafter

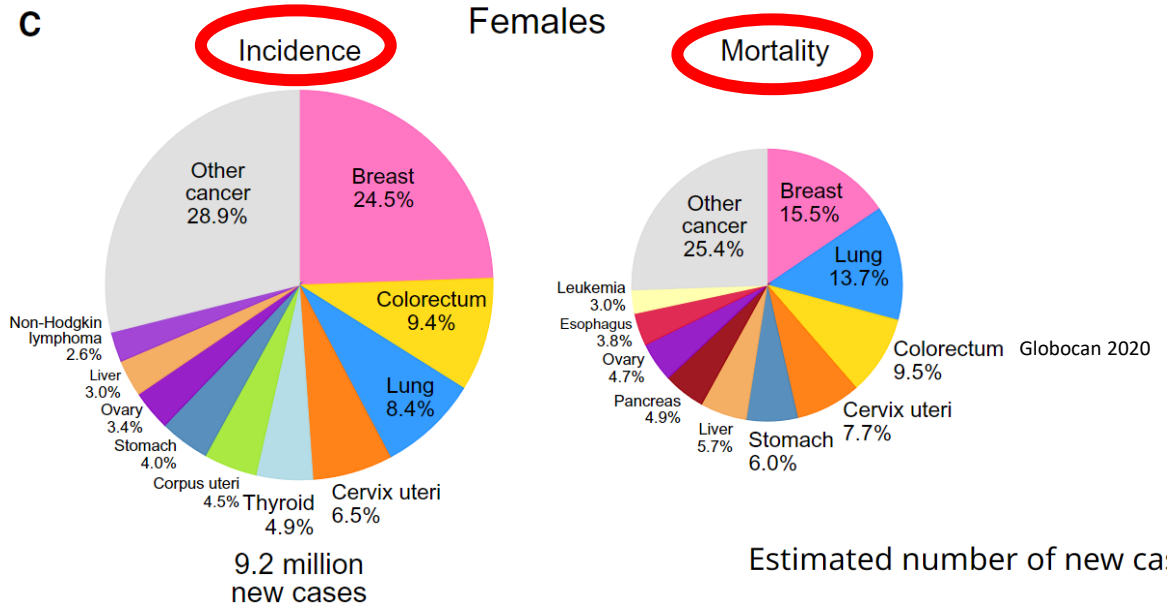
Rate of New HPV-associated Cancers by Cancer Type
All HPV-associated Cancers, Female, United States, 2014-2018

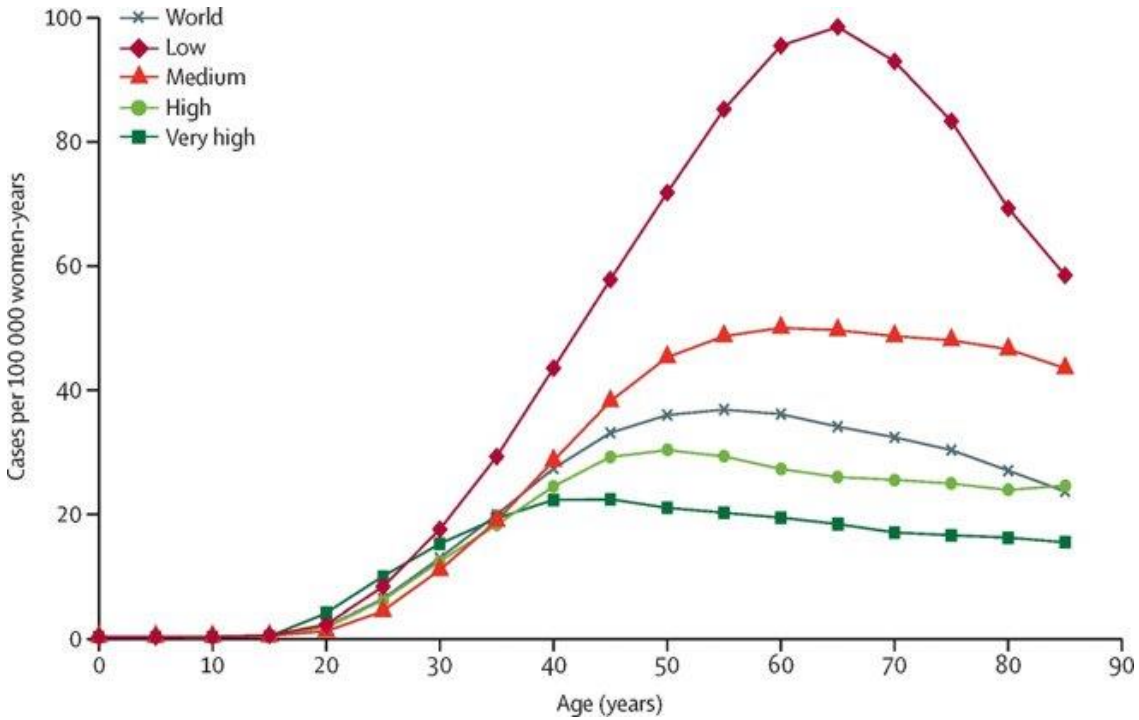


Rate per 100,000 women

Source - U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2020 submission data (1999-2018): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in June 2021.

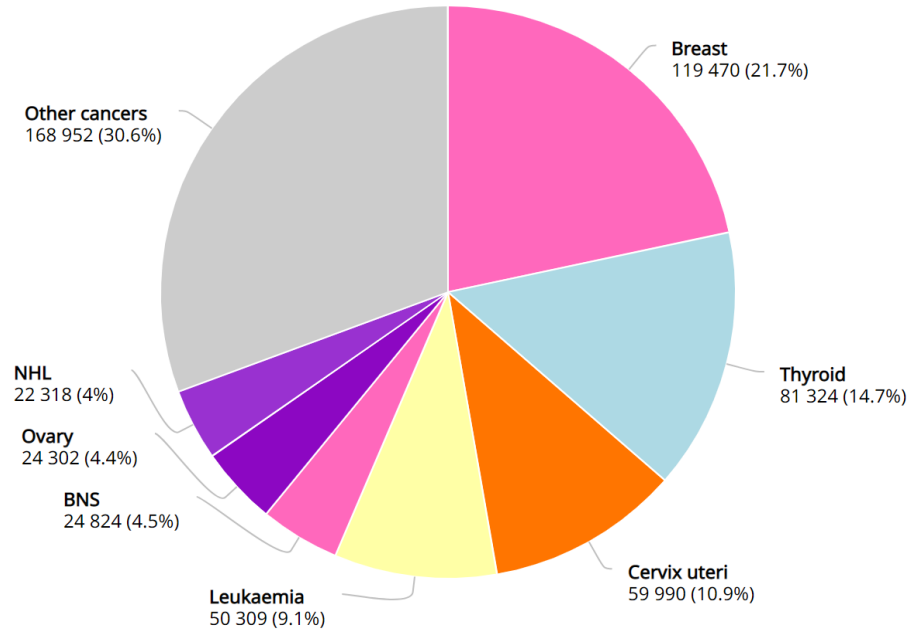






Arbyn et al. (2019). Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. The Lancet Global Health. 8

Estimated number of new cases in 2020, worldwide, females, ages 0-34

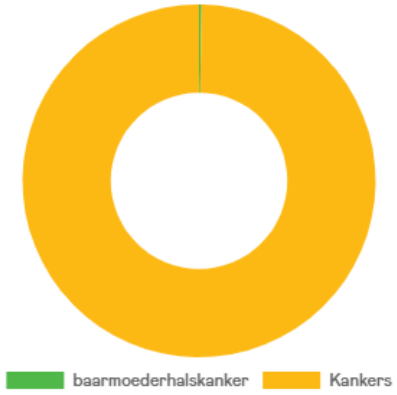


Total : 551 489

Data source:GLOBOCAN 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr/)

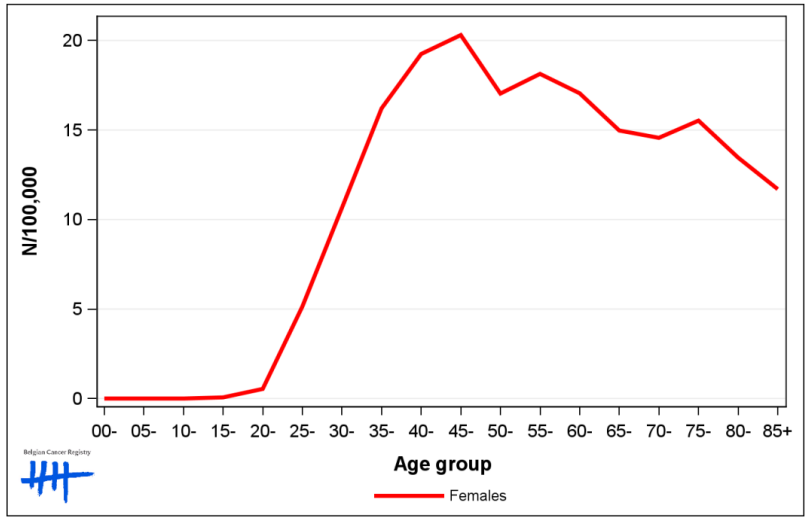
En in België?

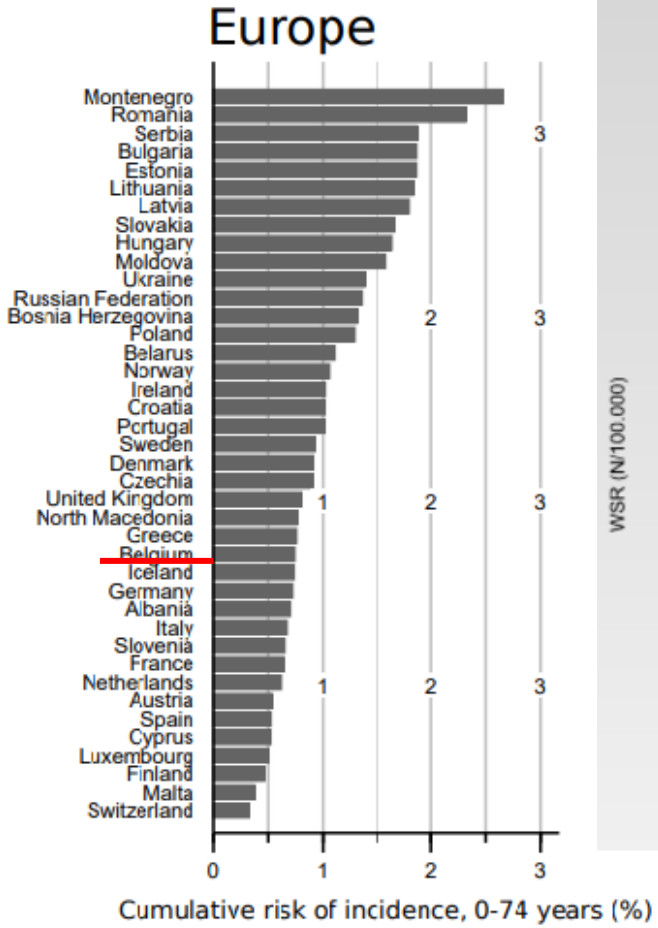
Baarmoederhalskanker is de **23e** meest voorkomende kanker in België .
In 2021, zijn **164** personen overleden ten gevolge van deze kanker in België.

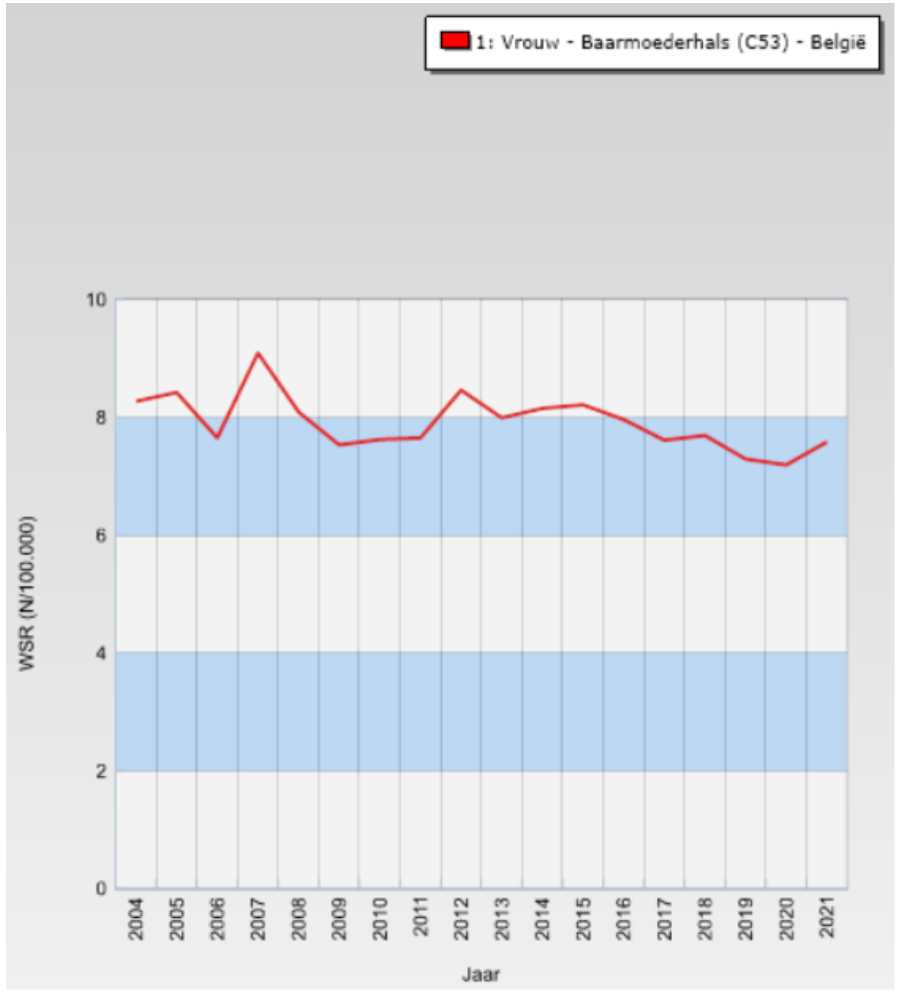


In 2022 waren er **76220** kankergevallen, waarvan* **641** baarmoederhalskankers (**0,84%**)

Figure 2: Cervical Cancer: Age-specific incidence rates, 2015-2019







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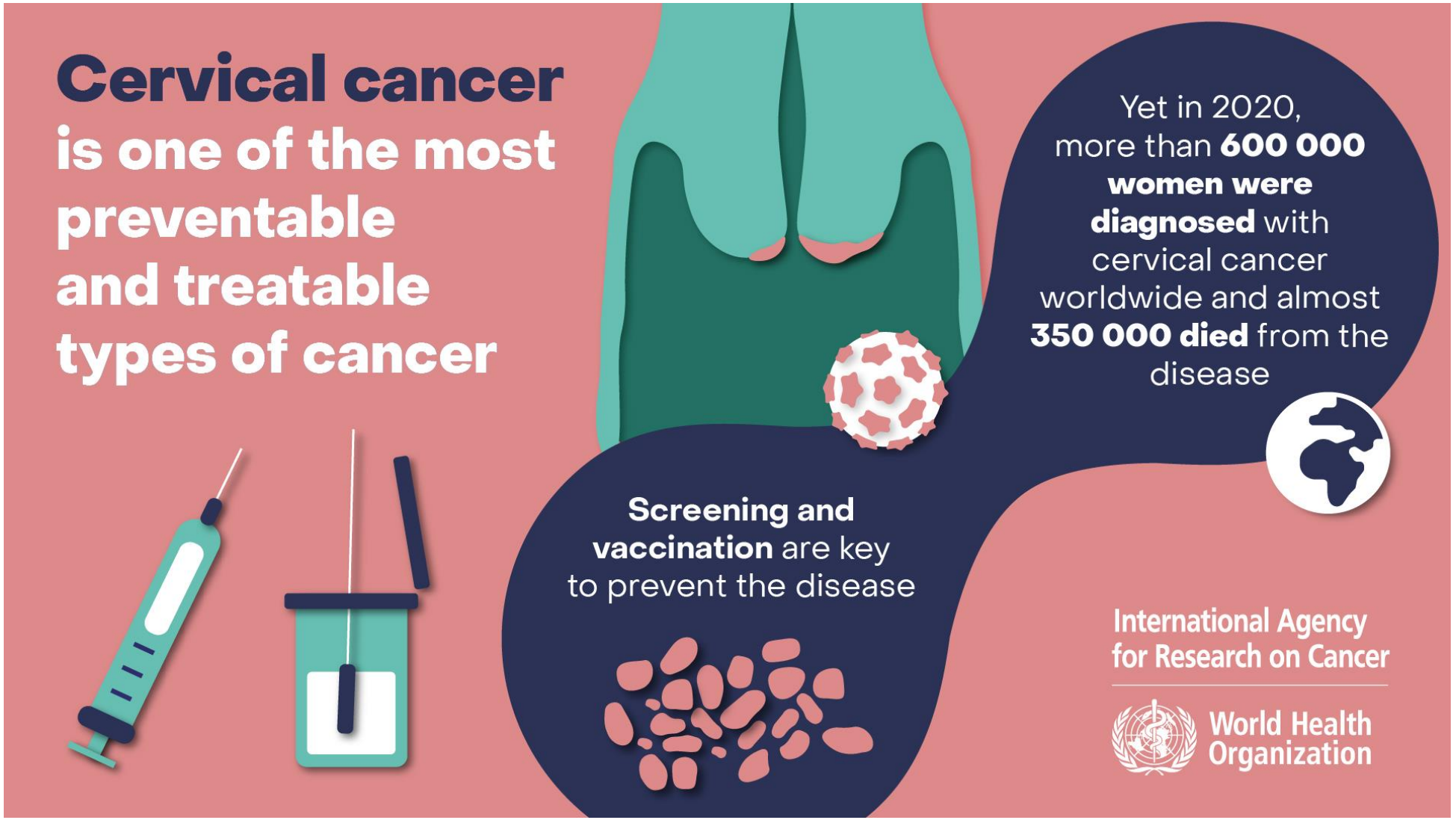


https://www.iarc.who.int/infographics/cervical-cancer-awareness-month-2022/

Wat is screening

Fig. 8. Balancing benefits and harm

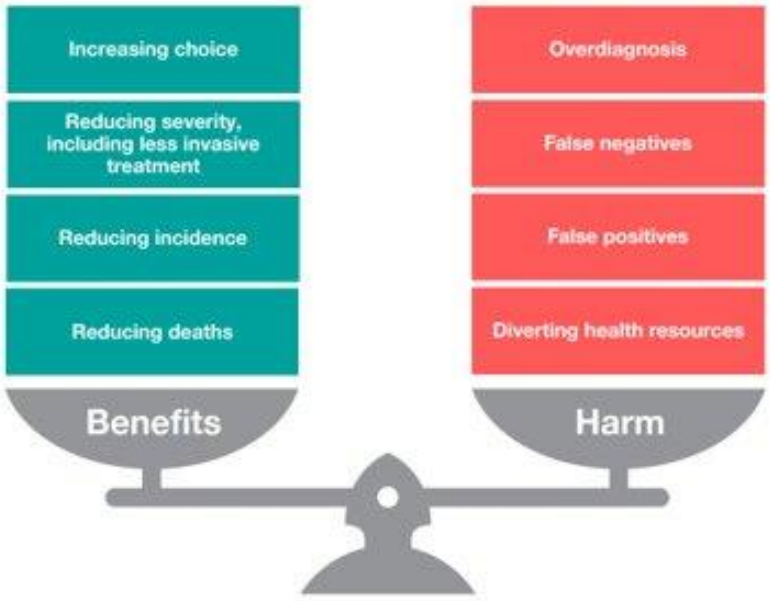


Fig. 3. Aims of screening programmes

The breast cancer screening programmes aims to reduce the ***mortality*** from breast cancer by the ***early detection*** and ***early treatment*** of asymptomatic cancers.

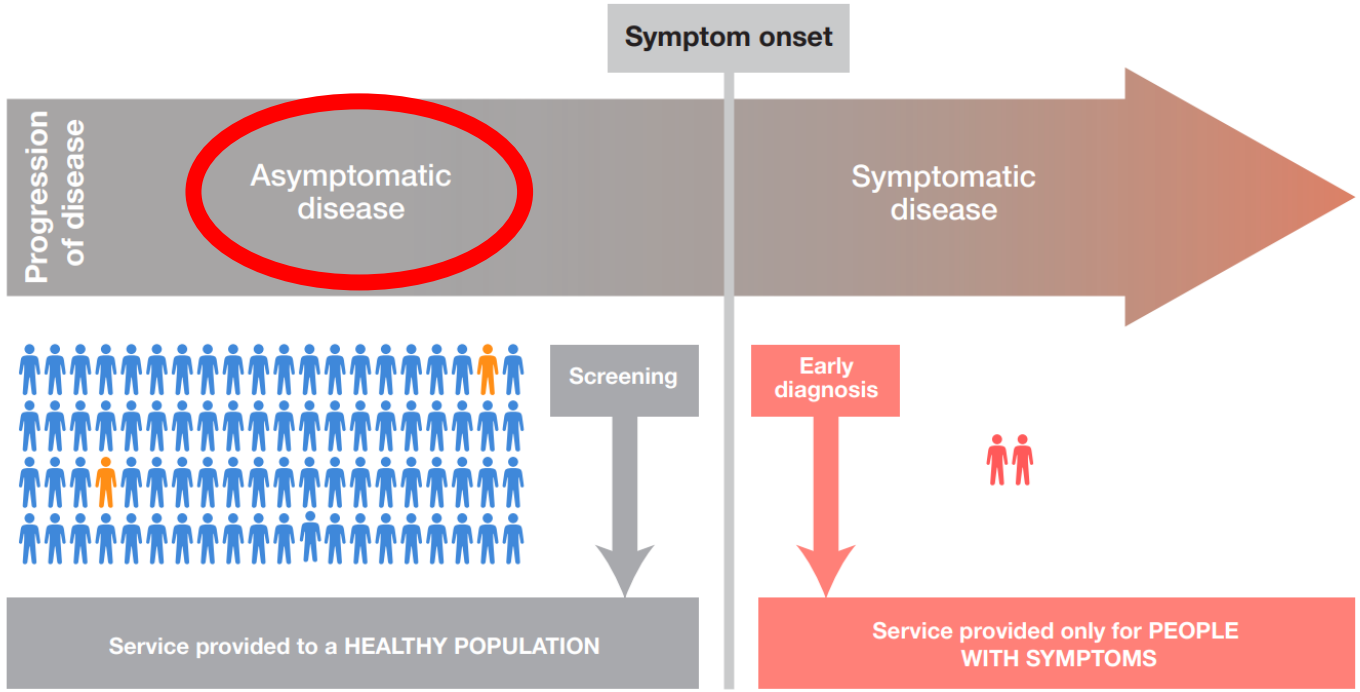
The cervical cancer screening programme aims to reduce the ***incidence*** and mortality of cervical cancer through the identification and treatment of precancerous stages of cervical cancer.

The diabetic retinopathy screening programme aims to ***reduce the severity of*** diabetic eye disease by early detection and treatment to prevent blindness.

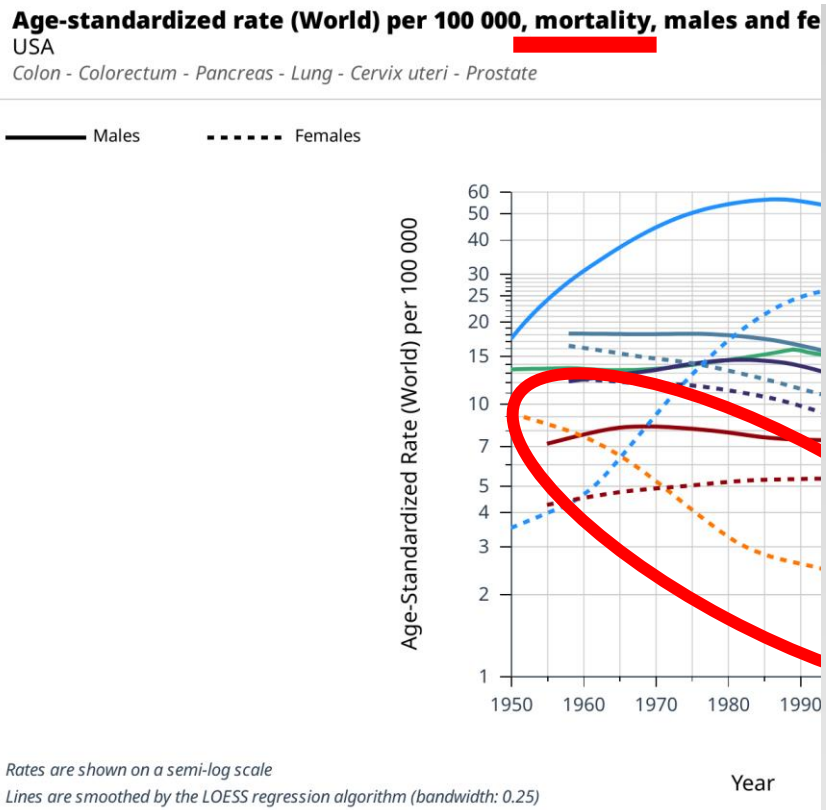
One aim of antenatal screening is to detect conditions in the fetus and provide information to parents so that they can make an ***informed choice*** about whether to continue or end a pregnancy.

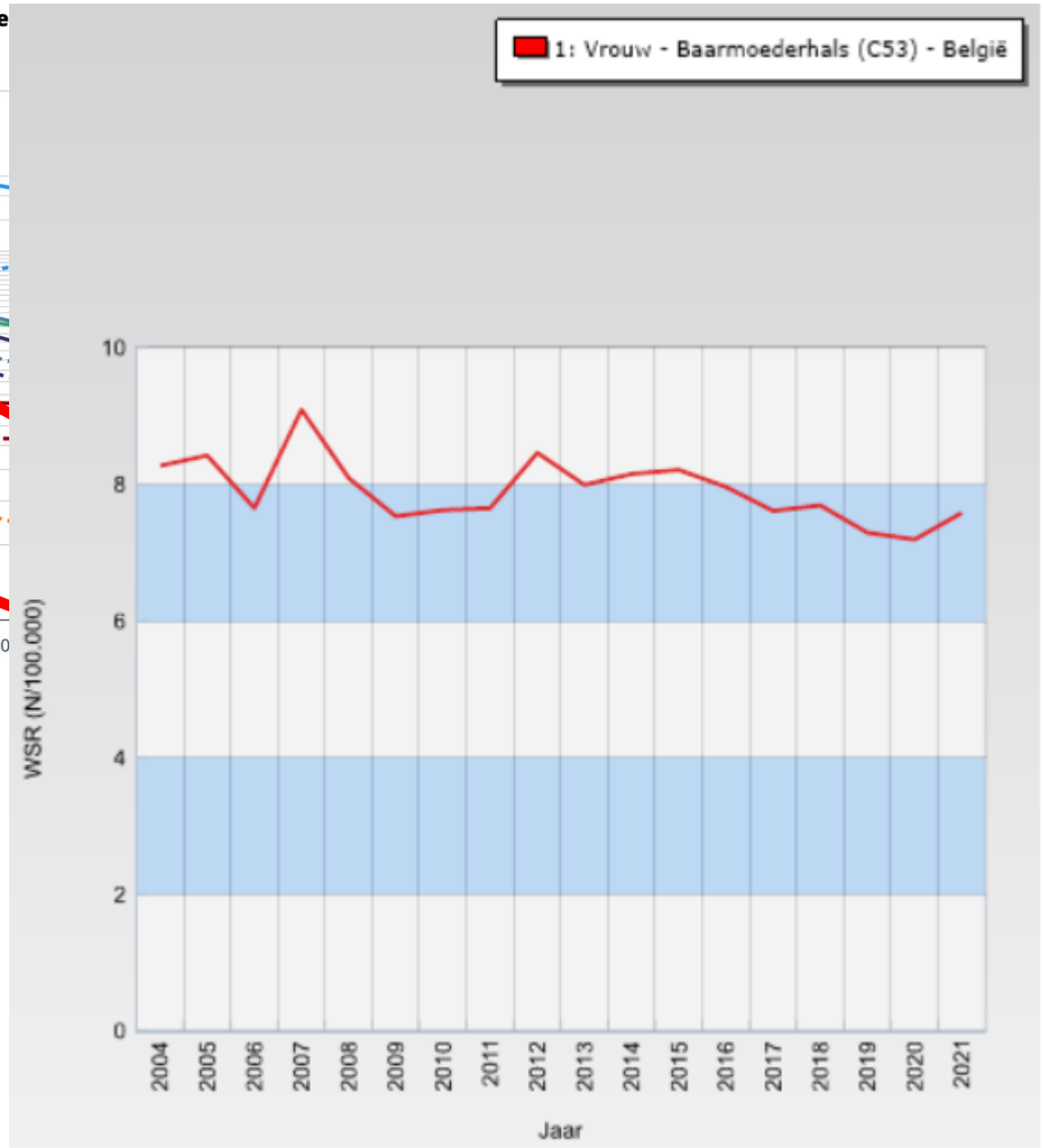
. Screening programmes: a short guide. Increase effectiveness, maximize benefits and minimize harm. Copenhagen: WHO Regional Office for Europe; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Fig. 2. Distinguishing screening from early diagnosis in cancer according to symptom onset



creening?


Age-standardized rate (World) per 100 000, mortality, males and fe
USA
Colon - Colorectum - Pancreas - Lung - Cervix uteri - Prostate
Males
Females
Age-Standardized Rate (World) per 100 000
Year
Rates are shown on a semi-log scale
Lines are smoothed by the LOESS regression algorithm (bandwidth: 0.25)
CANCER OVER TIME |IARC - All Rights Reserved 2022 - Data version: 1.0


1: Vrouw - Baarmoederhals (C53) - België
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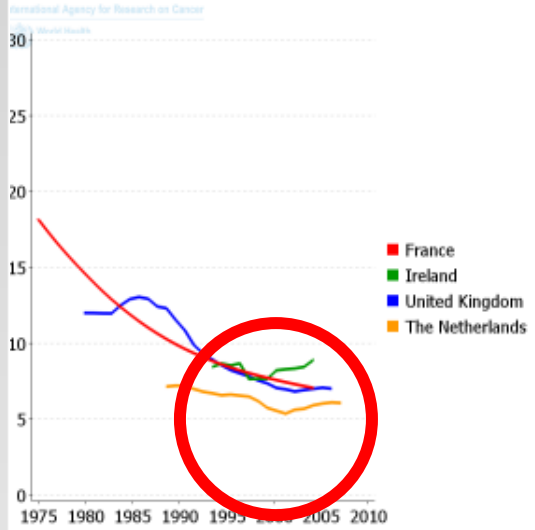
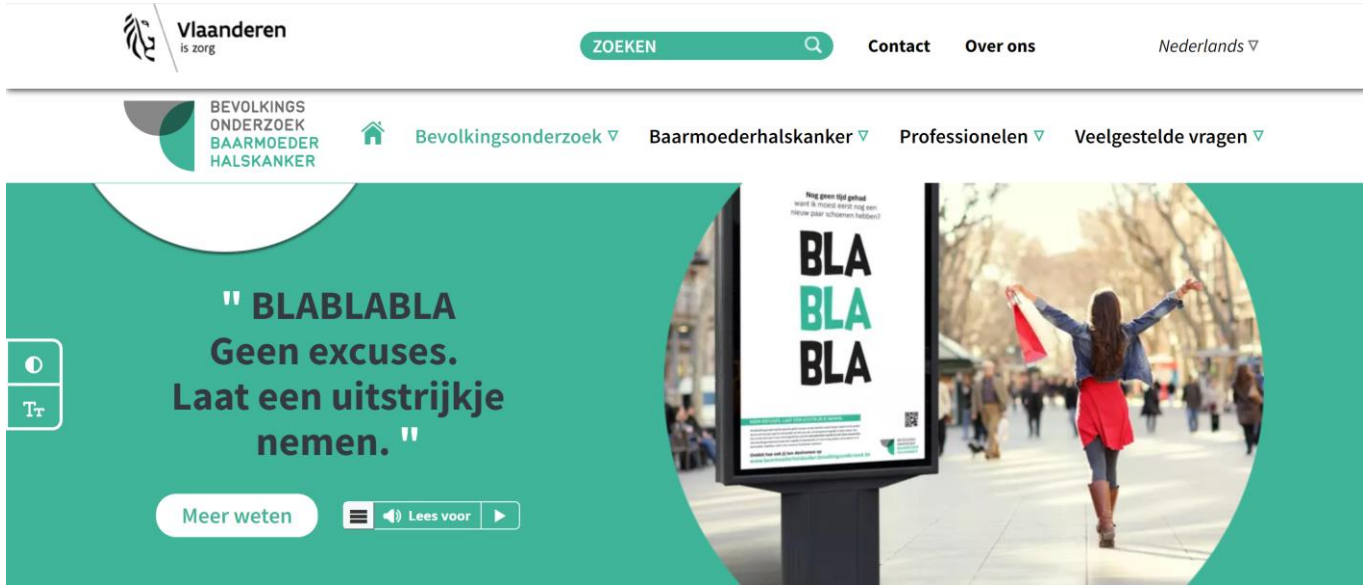
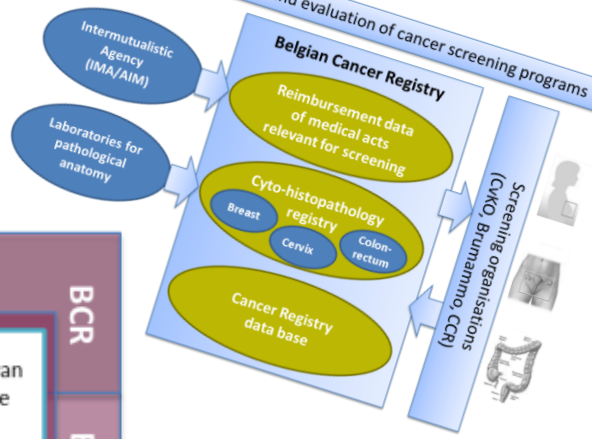

France
Ireland
United Kingdom
The Netherlands

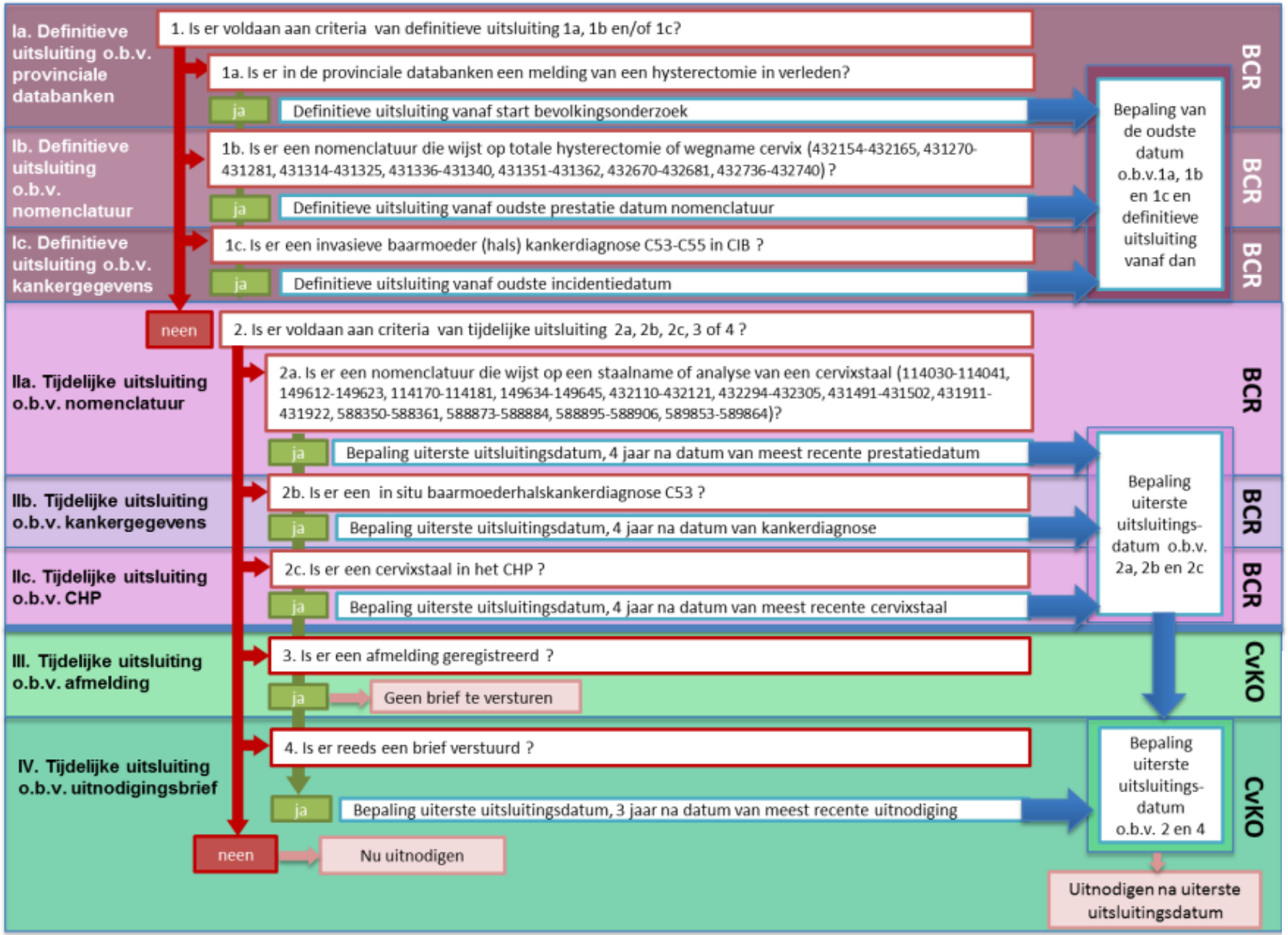
Screening België?



IMA • AIM
Intermutualistisch Agentschap

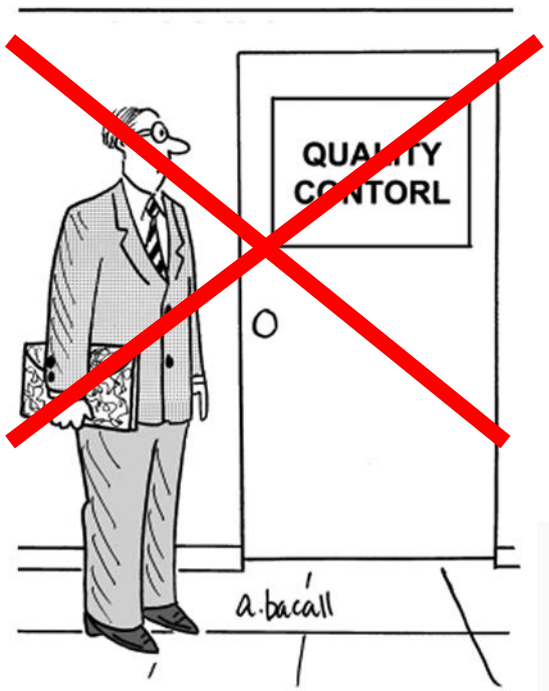
Algorithme uitnodiging





Belgian Cancer Registr

MAAR…


QUALITY
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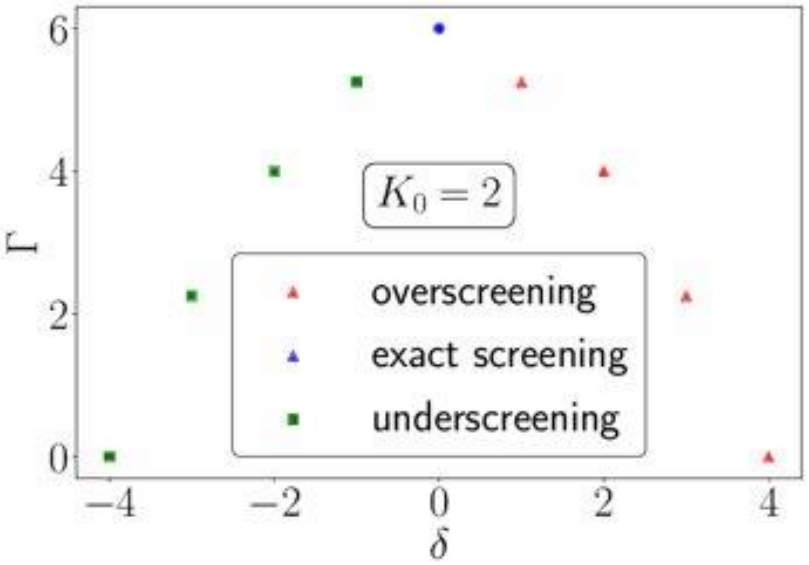
Gratis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exact screening
underscreening
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−2
0
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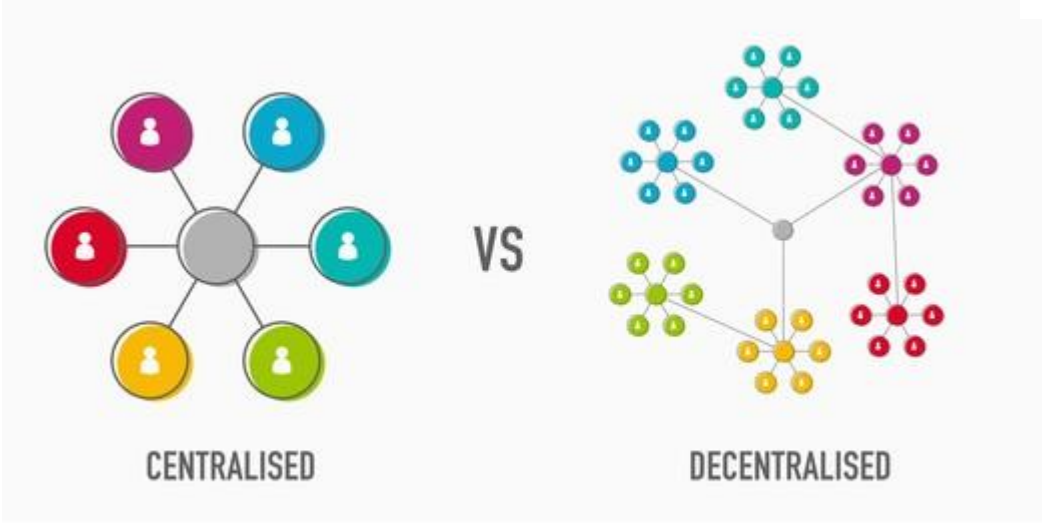
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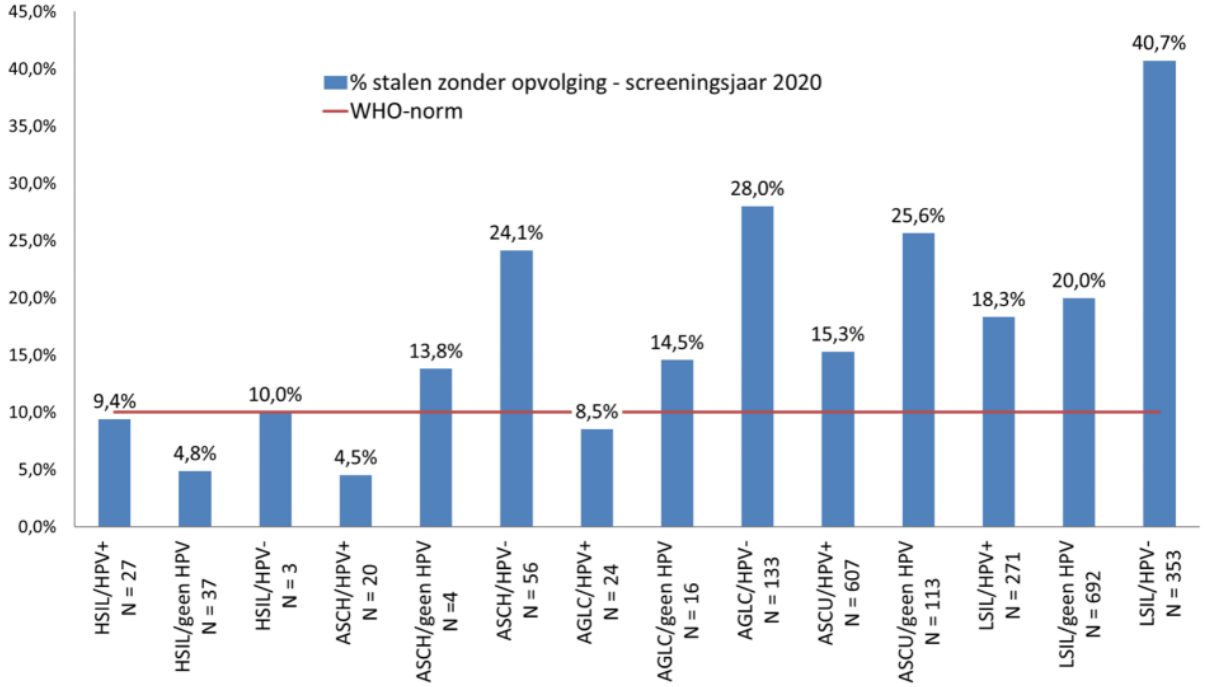
CENTRALISED
DECENTRALISED
shutterstock.com · 1852467046

Fail-safe procedure

Figuur 12: Aantal en percentage van afwijkende screeningsuitstrijkjes zonder opvolging binnen het jaar, opgesplitst per diagnose en HPV-resultaat voor screeningsjaar 2020



Tabel 5: Overzicht van de vrouwen geselecteerd voor faalveiligheid in 2019 en 2020 en de opvolging ervan in de loop van de verschillende stappen van het faalveiligheidsmechanisme

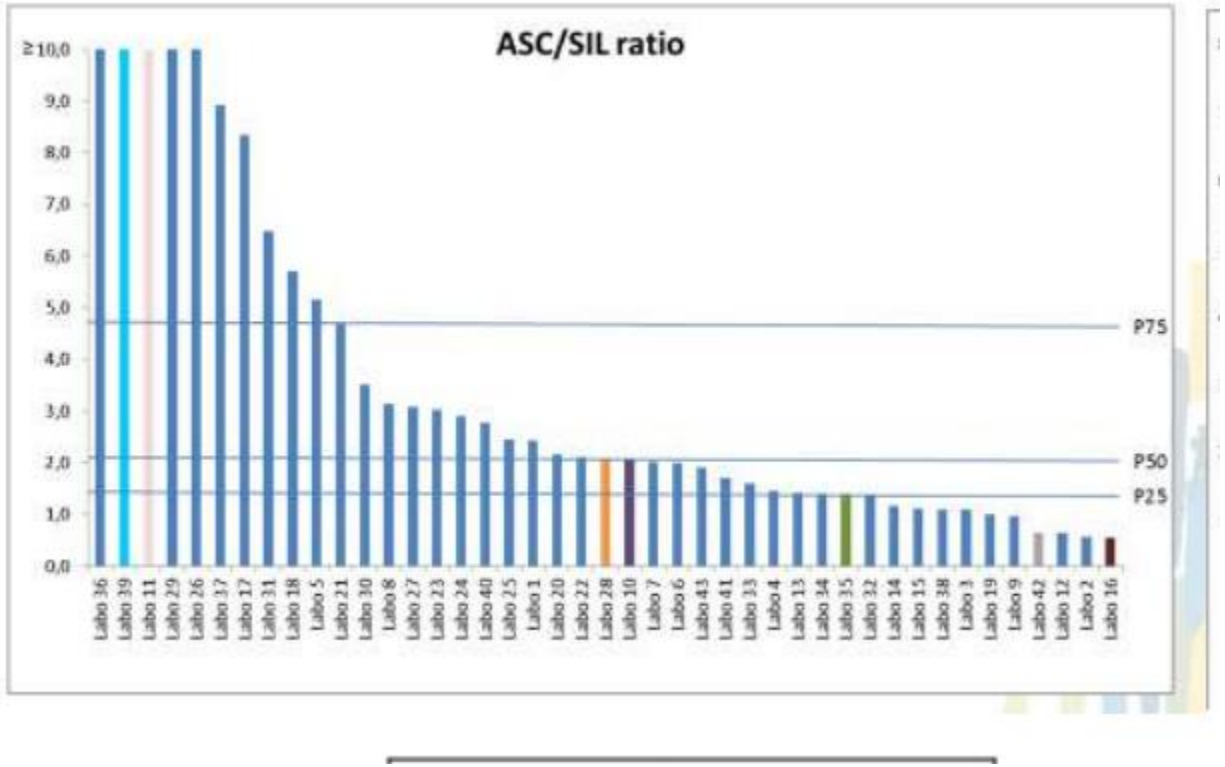
	2019		2020	
	Aantallen	%	Aantallen	%
Totaal aantal vrouwen geselecteerd voor faalveiligheid (a)	217	100,0%	283	100,0%
Aantal vrouwen geselecteerd voor faalveiligheid **zonder opvolging** (b)	52	24,0%	69	24,4%
Aantal vrouwen geselecteerd voor faalveiligheid **met opvolging** (c)	165	76,0%	214	75,6%
Opvolging **voor versturen van faalveiligheidsbrief (= overbodige faalveiligheidsbrief) (d)**	97	44,7%	105	37,1%
Opvolging **na het versturen van de faalveiligheidsbrief (e)**	68	31,3%	109	38,5%

Feedback rapport

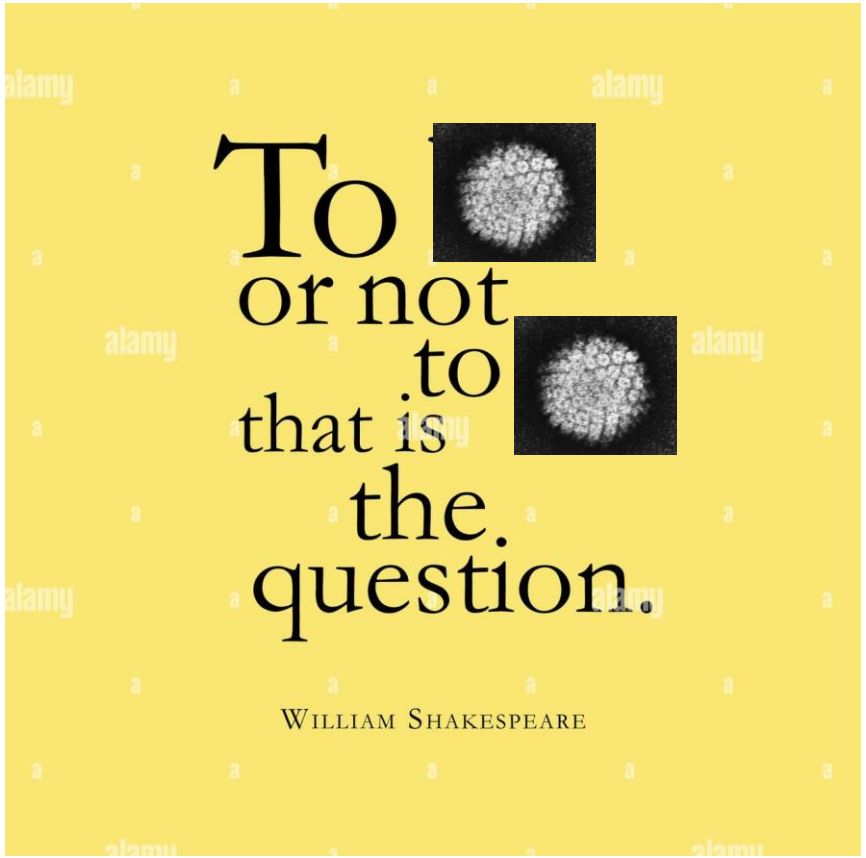
2.1.C. Dataset for test results of cervical/vaginal smears and biopsies

	Variable	Compulsory (C) Optional (O) Highly Recommended (HR)	Format	Short comment (for details see further)
1	INSZ/NISS	C	11 characters, text format without space	Leading zero's should be conserved! ('TEXT' format therefore necessary)
2	Last name	O/C	Free text field	Compulsory if INSZ/NISS unknown
3	First name	O/C	Free text field	Compulsory if INSZ/NISS unknown
4	Sex	C	Female F-M-U*	
5	Date of birth	C	yyyymmdd DD/MM/YYYY*	
6	Date of death	O	yyyymmdd DD/MM/YYYY*	Only if applicable
7	Postal code	C	Free text field	
8	Country code	C	2 characters, text format	ISO-code of the legal residence of the person
9	Specimen number	C	Free text field	Should match the specimen number in the protocol
10	Date specimen was taken	C	yyyymmdd DD/MM/YYYY*	
11	Requesting hospital/laboratory	O	Free text field	Name of the hospital/laboratory that requests the pathological examination.
12	RIZIV/INAMI number of the applicant of the test	C	11 numbers text format without space	
13	Quality of the specimen	C	SUF & INSU	Only for pap smears
14	Diagnostic procedure	HR	Free text field	Please provide the significance of your codes in a separate file/mail
15	Organ	C	Free text field	64XX, 65XX (Only use valid CODAP organ codes)**
16	Lesion	C	Free text field	All test results including negative tests, benign and premalignant lesions (Only use valid CODAP lesion codes or CERVIBASE)**
17	Degree of certainty (about lesion code)	O	1 = uncertain 2 = differential diagnosis 3 = certain	This field can be replaced by a comment field
18	HPV **high risk** test results	C if HPV test performed	HPV-, HPV+, HPVi	
19	HPV **high risk** types detected	C if genotyping performed	HP16, HP18, ... Free text field	Different HPV genotypes to be entered separated by commas ","
20	Nomenclature number(s)	O***	**Text format** without space	Different numbers to be entered separated by commas ","

O=Optional; C=Compulsory; O/C =Compulsory if INSZ/NISS unknown; HR=highly recommended
*This format is to be used when data will be transferred through the Healthdata.be-platform
** See also 'Coding manual For registration - CODAP version 2017' and 'Code Book CODAP version 2017' (http://kankerregister.org/downl-vr-pathologen)
*** From 01/01/2015 on, nomenclature numbers for cervical/vaginal samples are optional (Only applicable if certain conditions are fulfilled; see chapter 2.3.D)



Cervical cancer screening



Adapted from Hamlet, by William Shakespeare

The NEW ENGLAND JOURNAL of MEDICINE

UZ LEUVEN

SPECIAL REPORT

The IARC Perspective on Cervical Cancer Screening

Table 3. Comparative Effectiveness of the Established Cervical Cancer Screening Methods.*

Methods Compared	Comparison of angesBenefit-to-Harm Balances
HPV DNA testing vs. VIA	HPV DNA testing >> VIA
HPV DNA testing vs. cytology	HPV DNA testing > cytology
HPV DNA testing vs. cotesting†	HPV DNA testing ≥ cotesting

* The symbol >> indicates that the benefits of testing clearly outweigh the harms, the symbol > that the benefits outweigh the harms, and the symbol ≥ that the benefits do not outweigh the harms. VIA denotes visual inspection with acetic acid.

† Cotesting involves screening and cytologic analysis combined.

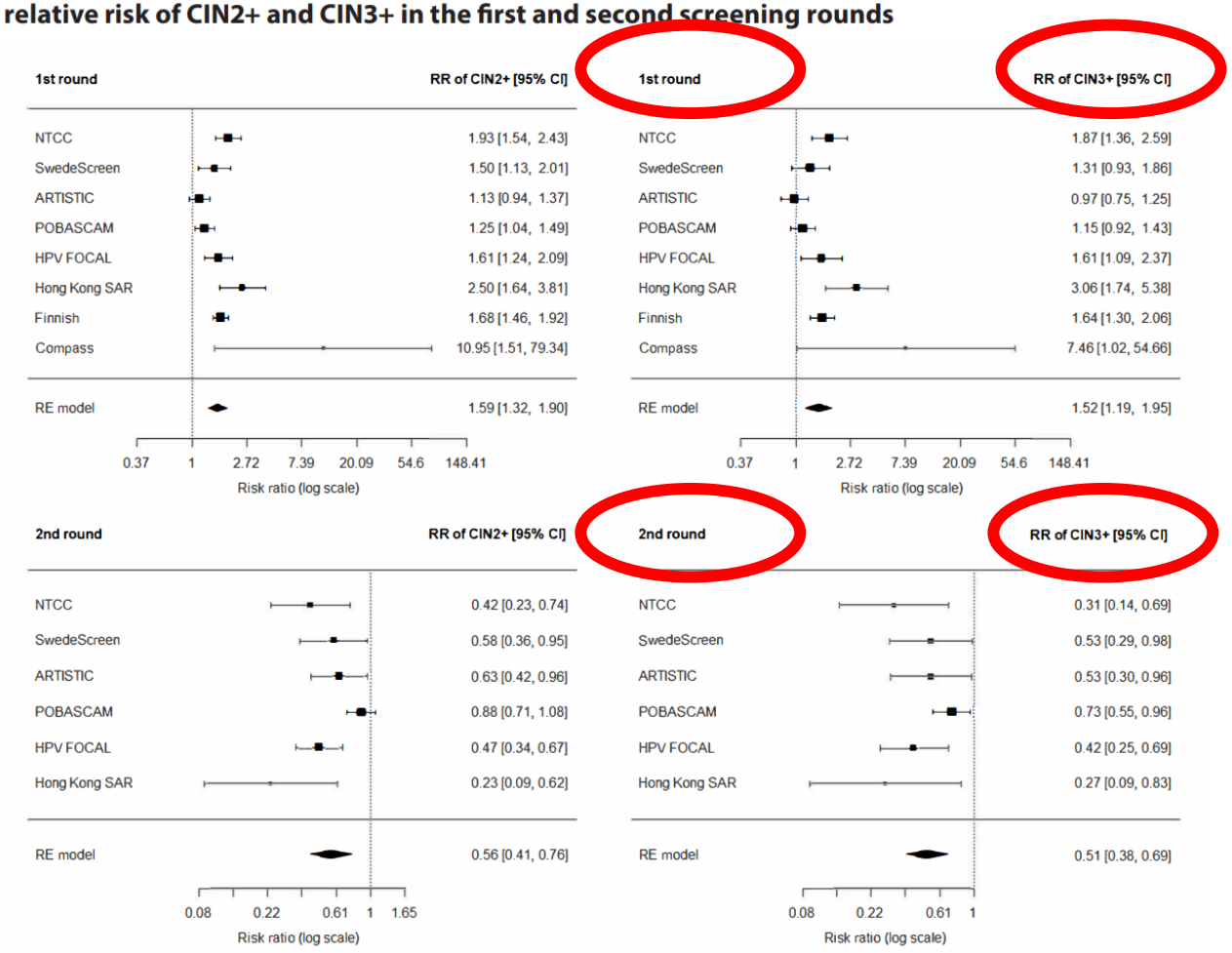
2018 USPSTF

This topic is being updated. Please use the link(s) below to see the latest documents available.

Update in Progress for Cervical Cancer: Screening

Waarom HPV?

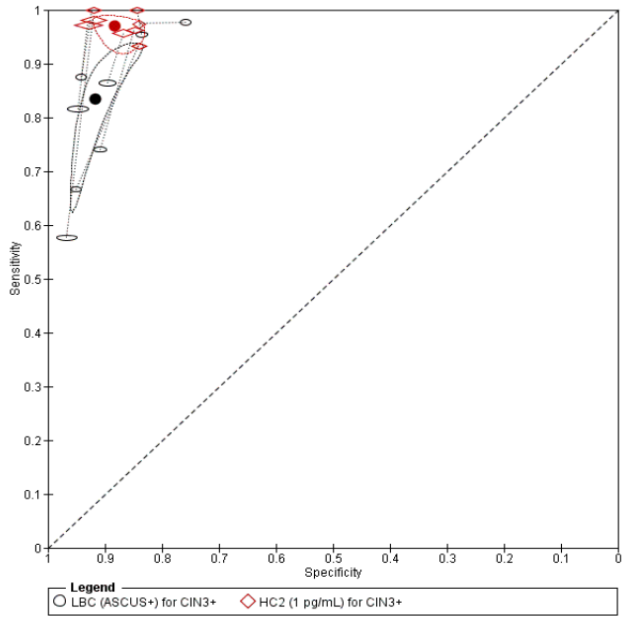
Fig. 4.4 Randomized controlled trials comparing HPV-based screening versus cytology screening: relative risk of CIN2+ and CIN3+ in the first and second screening rounds



cervical cancer screening IARC handbooks of cancer prevention volume 18 (2022)

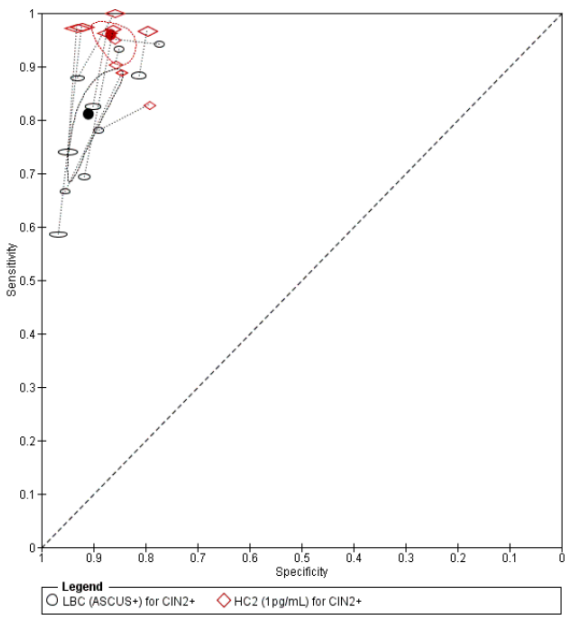
CIN 3

Figure 9. Summary ROC plot of 2 tests for detection of CIN 3+ (verified with histology): Liquid Based Cytology (LB (ASCUS+) and HPV testing with hybrid capture (HC) 2 (1pg/mL). The black and red solid circles correspond to the summary estimates of sensitivity and specificity, and are shown with a 95% confidence region.



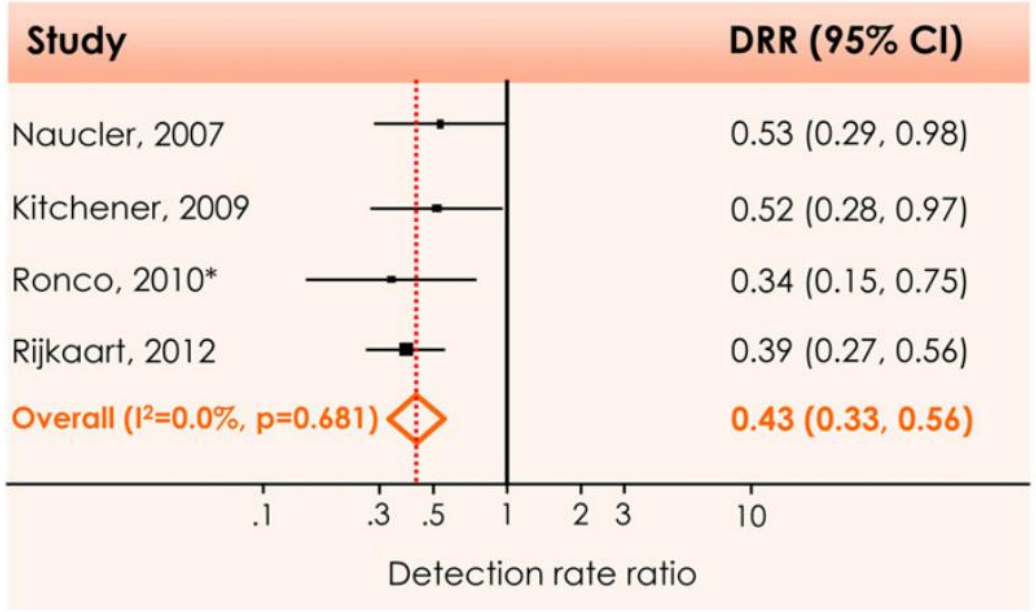
CIN 2

Figure 8. Summary ROC plot of 2 tests for detection of CIN 2+ (verified with histology): Liquid Based Cytology (LBC) (ASCUS+) and HPV testing with hybrid capture (HC) 2 (1pg/mL). The black and red solid circles correspond to the summary estimates of sensitivity and specificity, and are shown with a 95% confidence region.

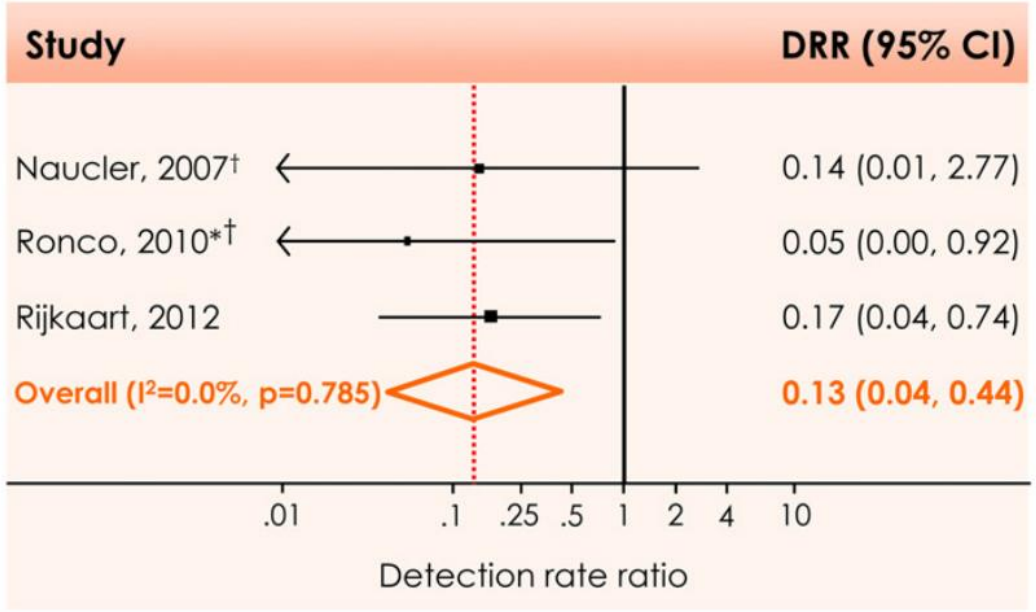


Koliopoulos et al. Cochrane Database of Systematic Reviews 2017, Issue 8

CIN3+



CERVICAL CANCER



* restricted to women of 35 years or older.
† continuity correction (+.5 in each cell because of zero cancer cases among HPV-negative women).

Arbyn et al. (2012). *Evidence Regarding Human Papillomavirus Testing in Secondary Prevention of Cervical Cancer. Vaccine, 30(), F88–F99.*

The HPV FOCAL Randomized Clinical Trial

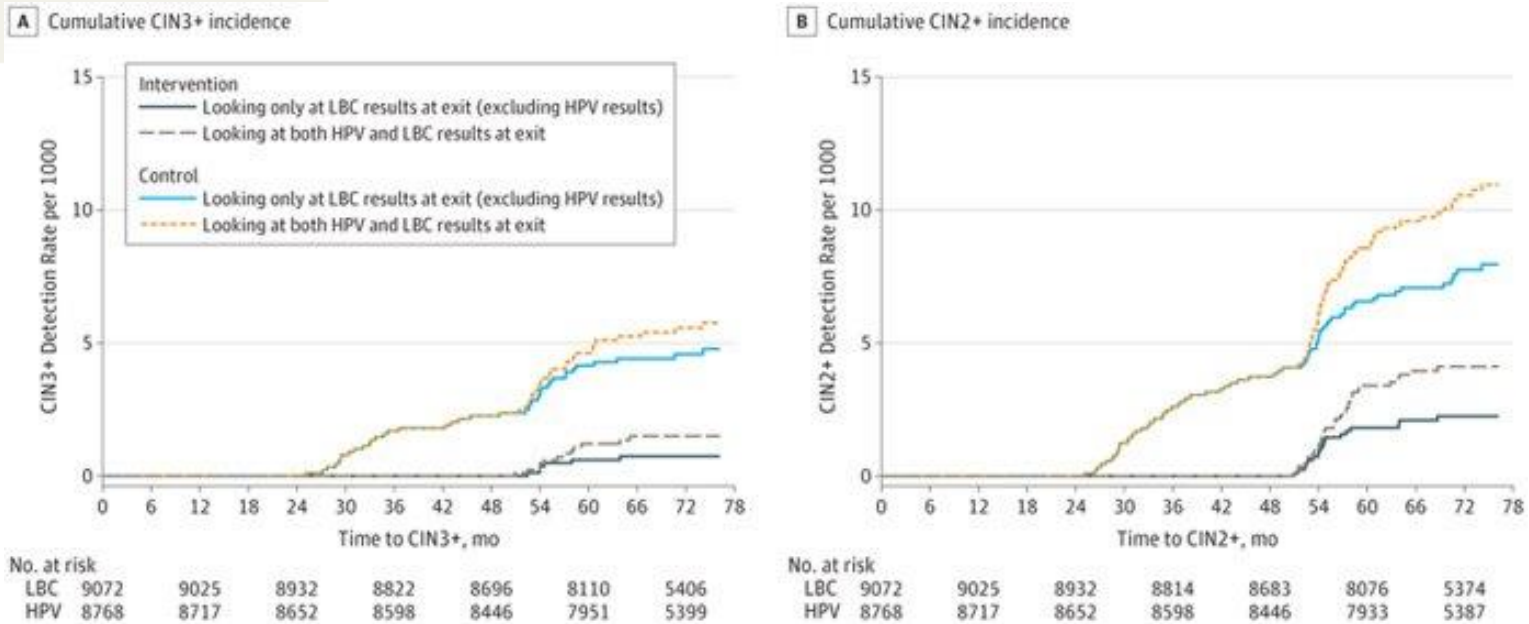
Key Points

Question Does cervical cancer screening using primary cervical human papillomavirus (HPV) testing compared with cytology result in a lower likelihood of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) at 48 months?

Findings In this randomized clinical trial that included 19 009 women, screening with primary HPV testing resulted in significantly lower likelihood of CIN3+ at 48 months compared with cytology (2.3/1000 vs 5.5/1000).

Meaning HPV-based screening resulted in lower likelihood of CIN3+ than cytology after 48 months, but further research is needed to understand long-term clinical outcomes as well as cost-effectiveness.

	All Participants			Baseline Negative Screen	
	Incidence Rate/1000 (95% CI) at 48 mo		Risk Ratio (95% CI)	Incidence Rate/1000 (95% CI) at 48 mo	Risk Ratio (95% CI)
	Intervention Group	Control Group			
CIN3+	2.3 (1.5-3.5)	5.5 (4.2-7.2)	0.42 (0.25-0.69)	1.4 (0.8-2.4)	0.25 (0.13-0.48)
CIN2+	5.0 (3.8-6.7)	10.6 (8.7-12.9)	0.47 (0.34-0.67)		



Ogilvie , et al. *JAMA.* 2018;320(1):43–52.

Wanneer?

Summary recommendation for the general population of women

WHO suggests using either of the following strategies for cervical cancer prevention among the general population of women:

- HPV DNA detection in a screen-and-treat approach starting at the **age of 30 years** with regular screening **every 5 to 10 years**.
- HPV DNA detection in a screen, triage and treat approach starting at the **age of 30 years** with regular screening **every 5 to 10 years**.

CONSENSUS STATEMENT

Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC)

- **Not below 25 yo**
- **<30 HPV versus Cyt = ?**
  - **Lower specificity**
  - **Triage needed**

These recommendations differ slightly from those given by ACS in 2012 and by the US Preventive Services Task Force (USPSTF) in 2018 .

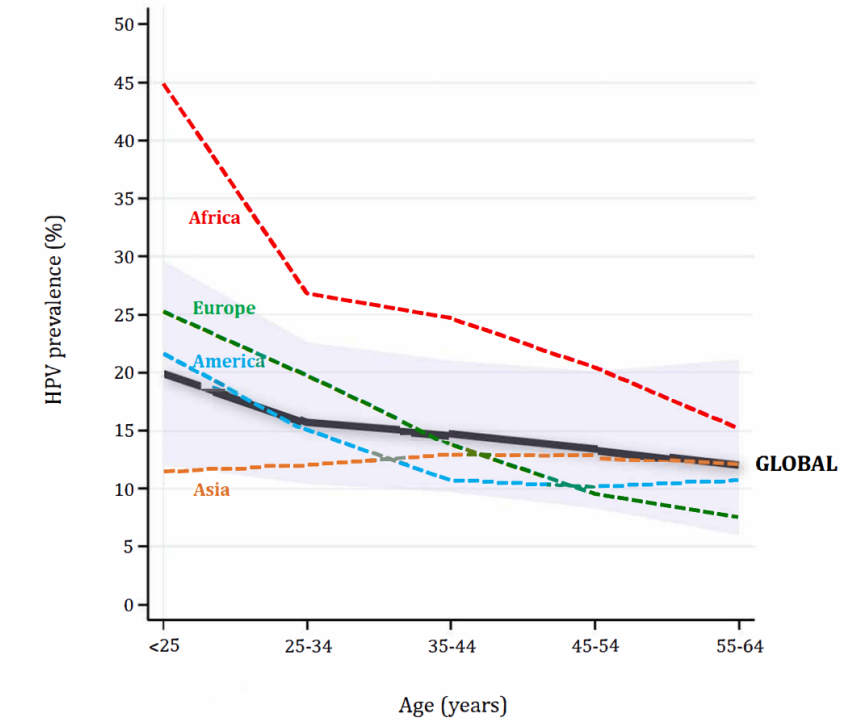
	2020 ACS	2012 ACS	2018 USPSTF
Age 21–24	No screening	Pap test every 3 years	Pap
Age 25–29	HPV test every 5 years (preferred) HPV/Pap cotest every 5 years (acceptable) Pap test every 3 years (acceptable)	Pap test every 3 years	Pap
Age 30–65	HPV test every 5 years (preferred) HPV/Pap cotest every 5 years (acceptable) Pap test every 3 years (acceptable)	HPV/Pap cotest every 3 years (preferred) Pap test every 3 years (acceptable)	Pap HP yea cot 5 y
Age 65 and older	No screening if a series of prior tests were normal	No screening if a series of prior tests were normal	No ser we at l cer

LAST UPDATED: Mar 10, 2022

An Update for This Topic is In Progress

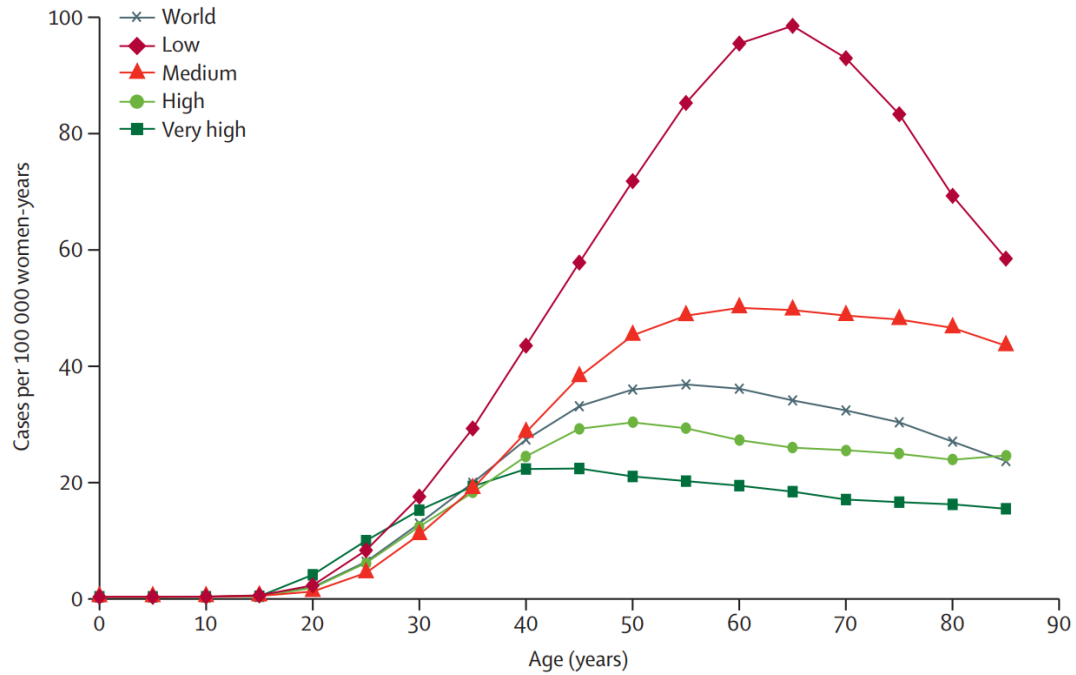
U.S. Preventive Services TASK FORCE

Fig. 1.8 Age-specific standardized prevalence of human papillomavirus (HPV) infection by world region



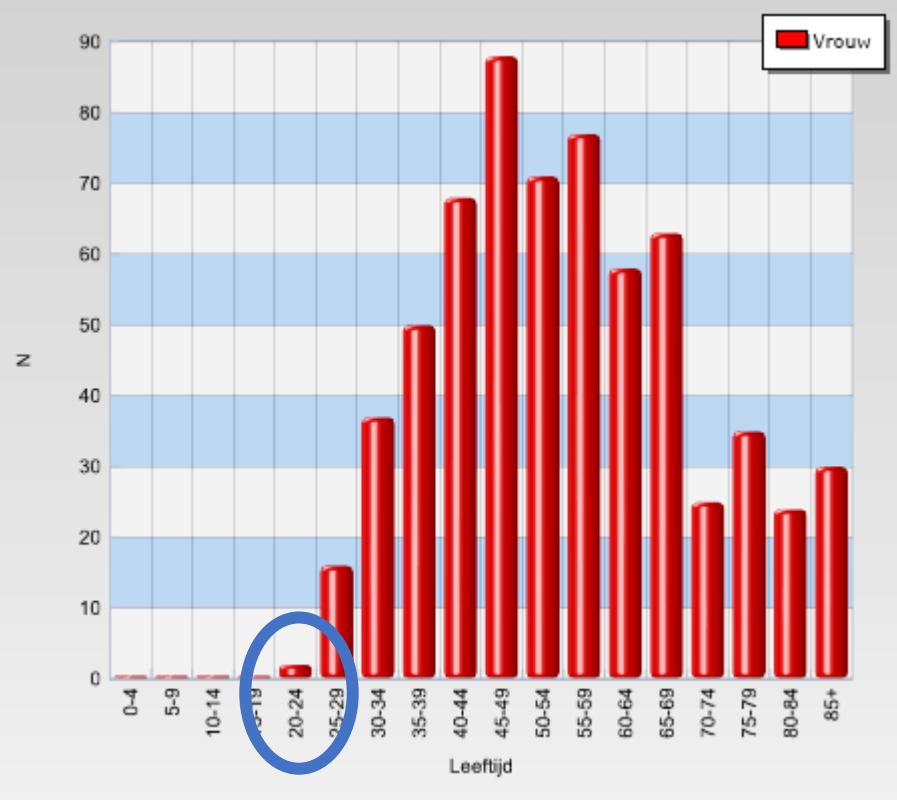
The shaded area represents the 95% confidence interval for the global HPV prevalence.
Courtesy of Laia Bruni, Bruni et al. (2016).

Fig. 1.4 Age-specific incidence of cervical cancer worldwide and in terms of the four-tier Human Development Index (HDI), 2018



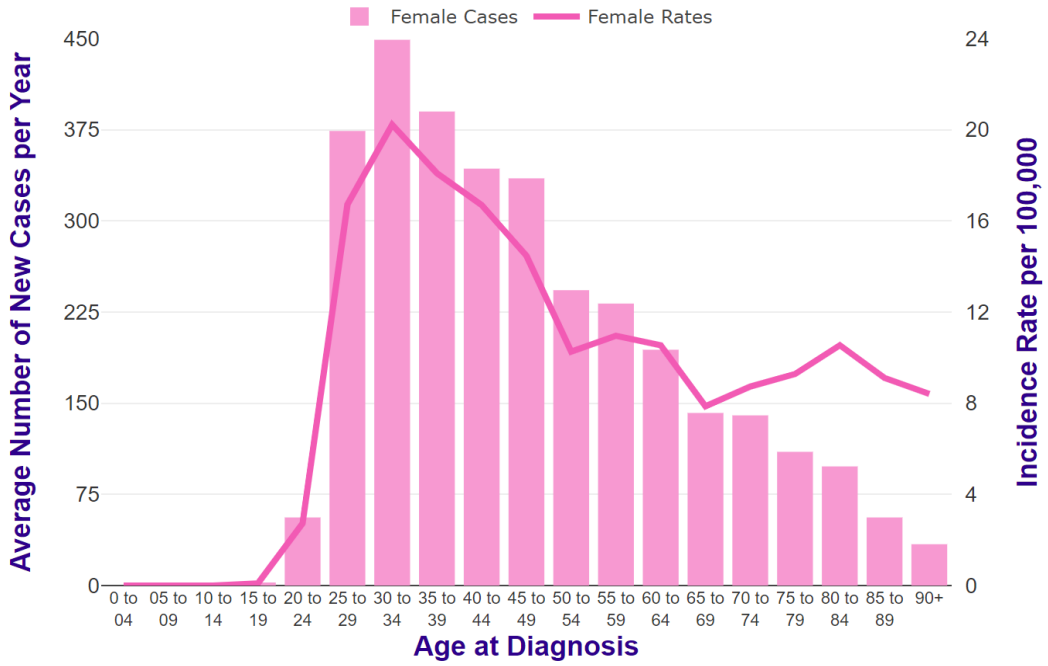
The four tiers of HDI are: low (< 0.55), medium (≥ 0.55 to < 0.7), high (≥ 0.7 to < 0.8), and very high (≥ 0.8).
Reproduced from Arbyn et al. (2020).

België 2018



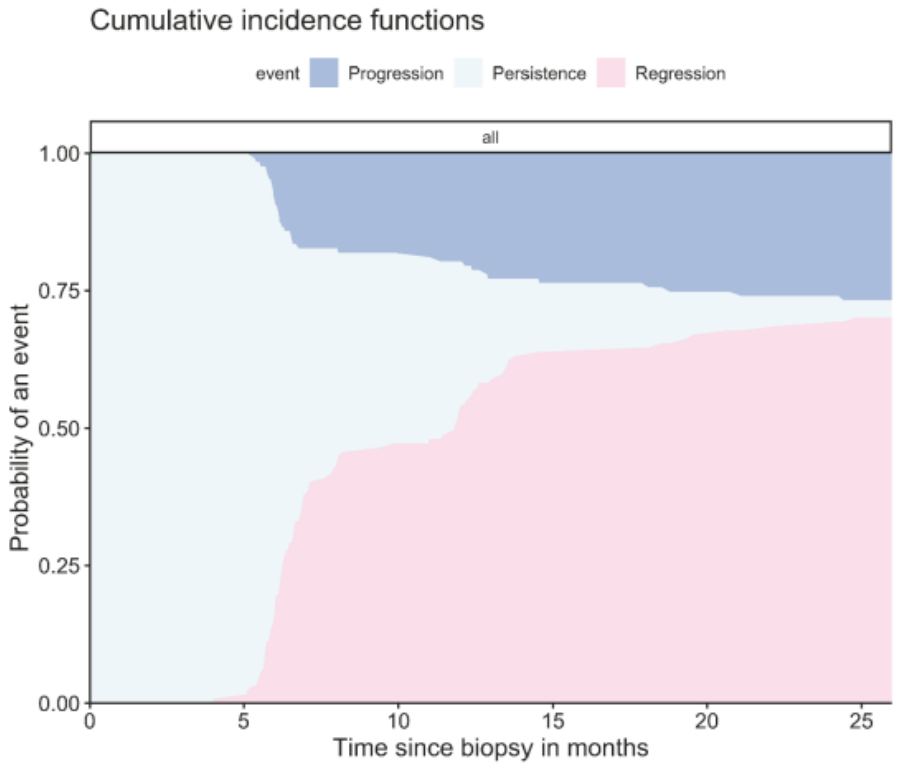
Kankerregister.org

Cervical cancer (C53), Average Number of New Cases per Year and Age-Specific Incidence Rates per 100,000 Female Population, UK, 2016-2018



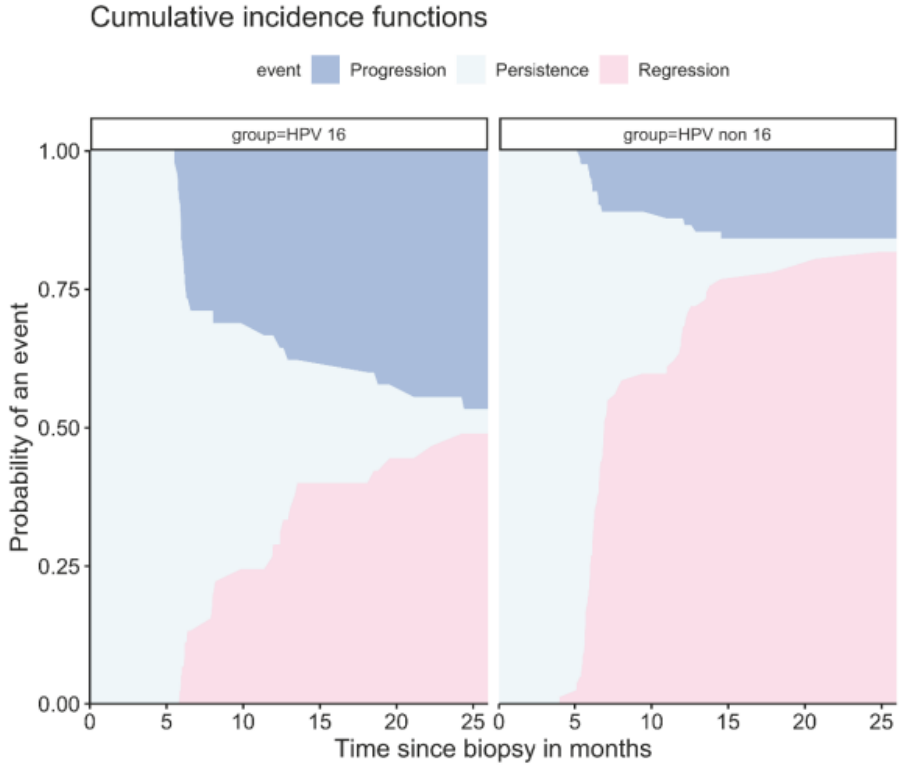
Cancerresearchuk.org

CIN 2 <30j



Cumulative incidence function (CIF), probability in percent for events 'Progression' and 'Regression' for Per protocol cohort (n=127).

	Progression (95% CI)	Regression (95% CI)
6 months	8.7 (4.6 - 14.3)	16.5 (10.7 - 23.5)
12 months	19.7 (13.3 - 27.0)	53.5 (44.5 - 61.8)
15 months	23.6 (16.7 - 31.3)	63.8 (54.8 - 71.5)
18 months	23.6 (16.7 - 31.3)	64.6 (55.6 - 72.2)
24 months	26.0 (18.7 - 33.8)	68.5 (59.7 - 75.8)



Cumulative incidence function (CIF), probability in percent for events 'Progression' and 'Regression' for group HPV16 and HPV-non16 for Per protocol cohort (n=127)

	Progression		Regression	
	HPV16 (95% CI)	*non-16 (95% CI)*	*HPV16 (95% CI)*	*non-16 (95% CI)*
6 months	15.6 (6.8 - 27.5)	4.9 (1.6 - 11.1)	4.4 (0.8 - 13.3)	23.2 (14.7 - 32.7)
12 months	33.3 (20.2 - 47.0)	12.2 (6.2 - 20.3)	28.9 (16.6 - 42.4)	67.1 (55.8 - 76.1)
15 months	37.8 (23.9 - 51.6)	15.9 (8.9 - 24.5)	40.0 (25.8 - 53.8)	76.8 (66.1 - 84.5)
18 months	37.8 (23.9 - 51.6)	15.9 (8.9 - 24.5)	40.0 (25.8 - 53.8)	78.0 (67.4 - 85.6)
24 months	44.4 (29.7 - 58.2)	15.9 (8.9 - 24.5)	46.7 (31.7 - 60.3)	80.5 (70.1 - 87.6)

Kyleba¨et al. Am J Obstet Gynecol 2022;227:742.e1-11

Welke HPV test?

Clinical Microbiology and Infection 27 (2021) 1083–1095

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Systematic review

2020 list of human papillomavirus assays suitable for primary cervical cancer screening

Marc Arbyn [1, 2, *], Marie Simon [3], Eliana Peeters [1], Lan Xu [1, 4], Chris J.L.M. Meijer [5], Johannes Berkhof [6], Kate Cuschieri [7], Jesper Bonde [8], Anja Ostrbenk Vanlencak [9], Fang-Hui Zhao [10], Remila Rezhake [1, 10, 11], Murat Gultekin [12], Joakim Dillner [13], Silvia de Sanjosé [14], Karen Canfell [15, 16], Peter Hillemanns [17], Maribel Almonte [18], Nicolas Wentzensen [19, †], Mario Poljak [9, †]

Human Papillomvirus	APTIMA HPV 16 18/45 Genotype Assay	Gen-Probe, Inc.	P120007 S001-S010
	APTIMA HPV Assay	Gen-Probe, Inc.	P100042 S001-S012
	BD ONCLARITY HPV ASSAY	BECTON, DICKINSON AND COMPANY	P160037
	cobas HPV for use on the cobas 6800/8800 Systems	Roche Molecular Systems, Inc	P190028
	Cervista HPV 16/18	Hologic, Inc.	P080015;S001-S012
	Cervista HPV HR and Genfind DNA Extraction Kit	Hologic, Inc.	P080014 S001-S018
	COBAS HPV Test	Roche Molecular Systems, Inc.	P100020 S001-S024
	Digene Hybrid Capture 2 High-Risk HPV DNA Test	Digene Corporation	P890064 S001-S034

Test	**Fabrikant**
Alinity m HR HPV Assay	Abbott, Wiesbaden, Duitsland
Allplex II HPV HR Detection	Seegene, Seoul, Zuid-Korea
Anyplex II HPV HR Detection	Seegene, Seoul, Zuid-Korea
APTIMA HPV Assay*	Hologic, Bedford, MA, USA
*in combinatie met een andere mRNA test (APTIMA HPV16, 18, 45; Hologic) welke HPV16 en HPV18,45 kan identificeren.	
CLART HPV4S	GENOMICA SAU, Madrid, Spanje
Cobas 4800 HPV Test	Roche Molecular System, Pleasanton, CF, USA
Cobas® HPV test (Voor gebruik Cobas® 5800/6800/8800 Systemen)	Roche Molecular System, Pleasanton, CF, USA
HPV-Risk Assay	Self-Screen BV, Amsterdam, Nederland
HPV Test Onclarity HPV Assay	BD Diagnostics, Sparks, MD, USA
NeuMoDX	Qiagen, Ann Arbor, MI, USA
RealTime High Risk HPV Test	Abbott, Wiesbaden, Duitsland
RIATOL HPV genotyping qPCR assay	in house, AML, Antwerpen, België
Xpert HPV	Cepheid, Sunnyvale, CA, USA

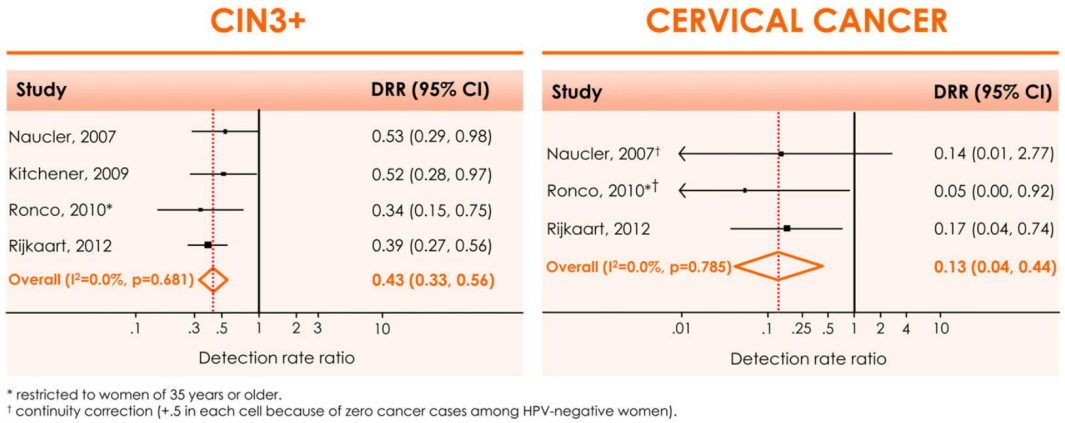
Lijst van internationaal gevalideerde hrHPV-tests voor screening op baarmoederhalskanker in België (alfabetisch gerangschikt).
Updated op 05/08/2024.

DISCLAIMER: Deze voorlopige lijst bevat de internationaal gevalideerde HPV-testen die door het NRC-HPV geschikt worden geacht, voor zover ons bekend, voor gebruik in de Belgische screening naar baarmoederhalskanker, op datum van publicatie van deze kennisgeving. Deze kennisgeving is echter geen officiële richtlijn over dit onderwerp. Sciensano kan niet aansprakelijk worden gesteld voor eventuele verschillen tussen deze kennisgeving en de BELAC-richtlijnen die over dit onderwerp zullen worden aangenomen, of andere toekomstige, gerelateerde officiële kennisgevingen.


JA.....
MAAR

Wat met HPV negatieve kanker?

NON-ISSUE



* restricted to women of 35 years or older.
† continuity correction (+.5 in each cell because of zero cancer cases among HPV-negative women).

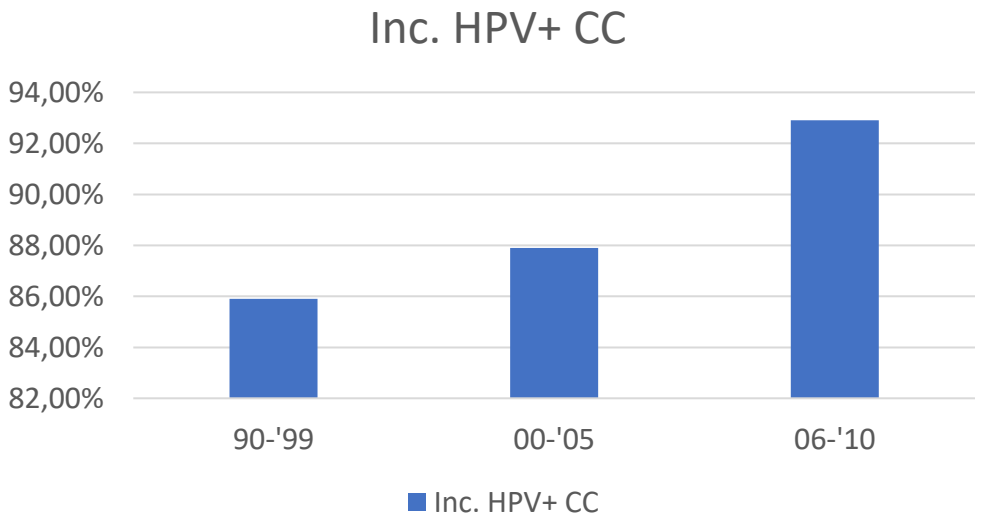
ADENO! HPV neg??

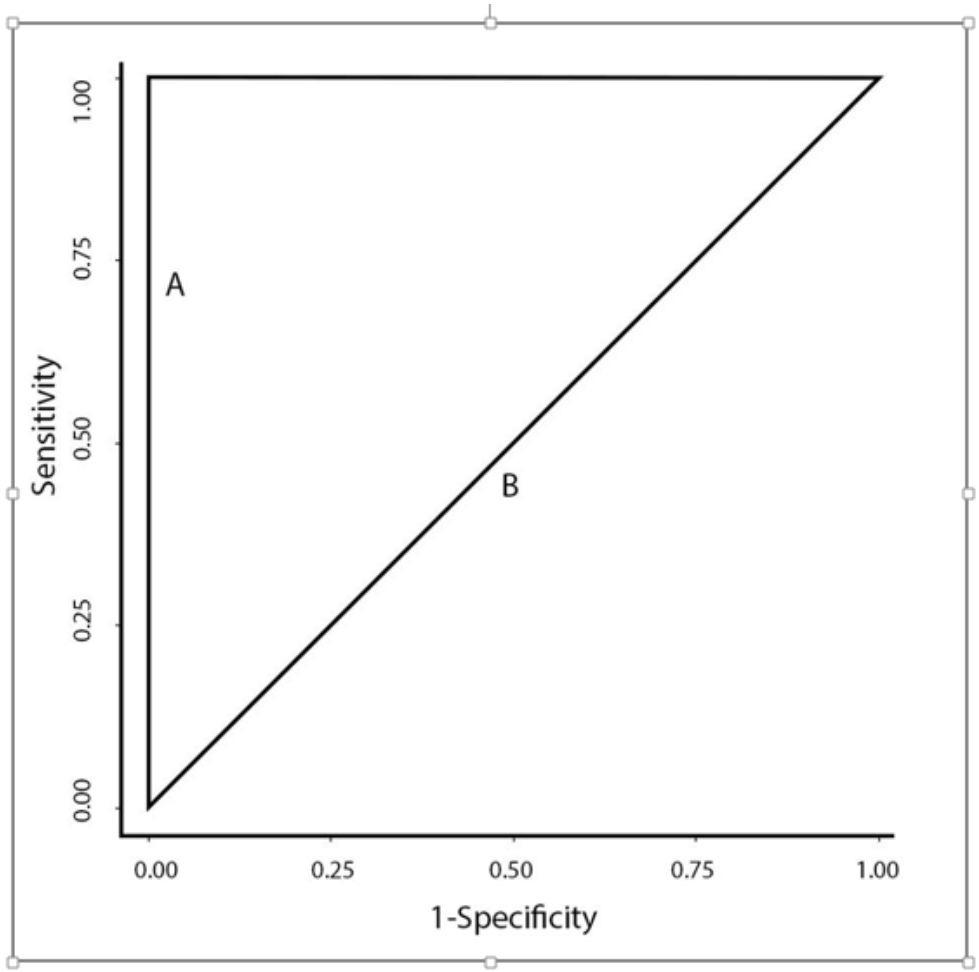
TABLE 2 | Pathological types of cervical adenocarcinoma and its human papillomavirus (HPV)-positive rate.

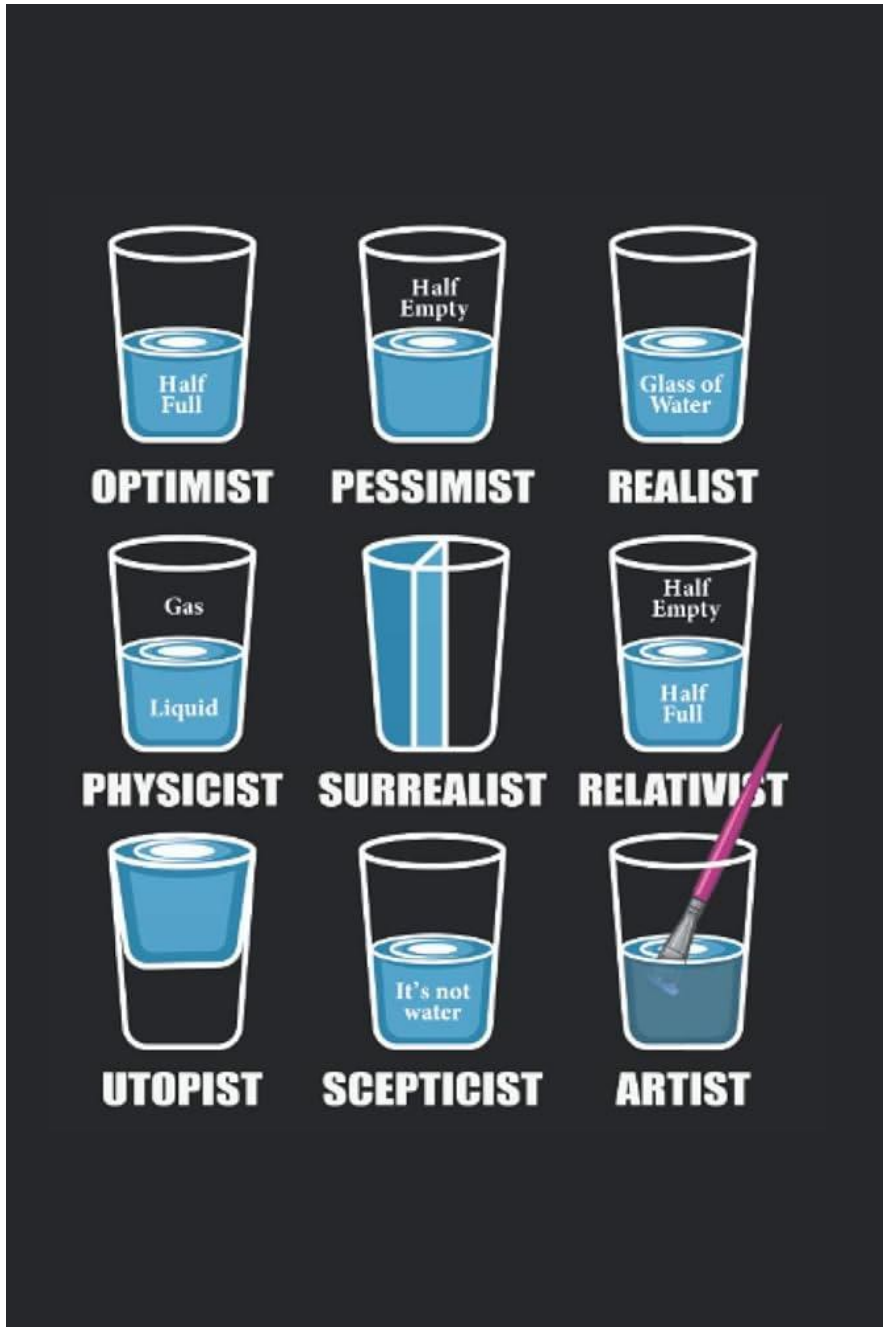
Pathological types (Reference)	Percentage of cervical adenocarcinoma, %		HPV-positive rate, % (17)
Endocervical (usual) type (15, 18)	73–79	**85%**	80–100
Intestinal (15)	3–8		83–100
Villoglandular (15)	0.8–6		100
Signet-ring cell (15)	0.3		100
Endometrioid (13, 15)	1.1–1.6		27.3
-From squamous columnar junction zone	—		100
-From upper endocervix and lower uterine segment	—		0
Gastric (15, 18)	1.5–10		0
Clear cell (13, 18)	4.4–6.3		20–27.6
Serous (13, 15)	0.5–3.5		25–30.4
Mesonephric (15)	0.3		0

Xing et al. (2021). Front. Oncol. 10:606335. doi: 10.3389/fonc.2020.606335

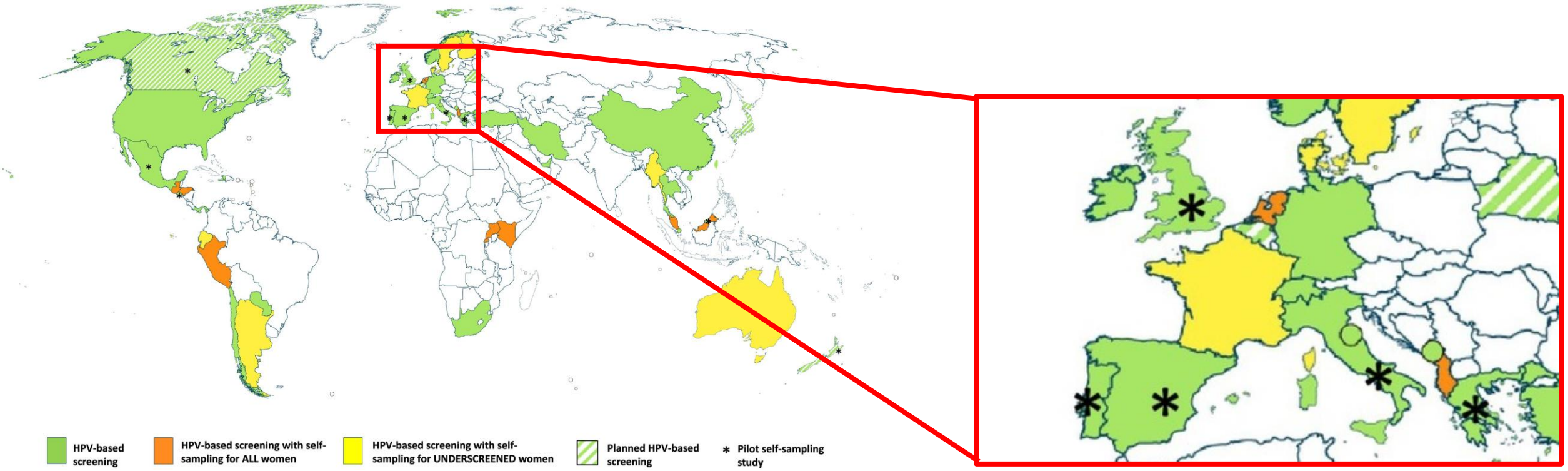
- Non cervical cancer?
- Test Sensitivity?
- Non High risk HPV?
- Loss of HPV DNA fragments? (ex. L1 test)




Sensitivity
1.00
0.75
0.50
0.25
0.00
A
B
0.00
0.25
0.50
0.75
1.00
1-Specificity


Half Full
OPTIMIST
Half Empty
PESSIMIST
Glass of Water
REALIST
Gas
Liquid
PHYSICIST
SURREALIST
Half Empty
Half Full
RELATIVIST
UTOPIST
It's not water
SCEPTICIST
ARTIST

Wie gebruikt HPV?



Serrano et al. Worldwide use of HPV self-sampling for cervical cancer screening, Preventive Medicine,Volume 154, 2022,

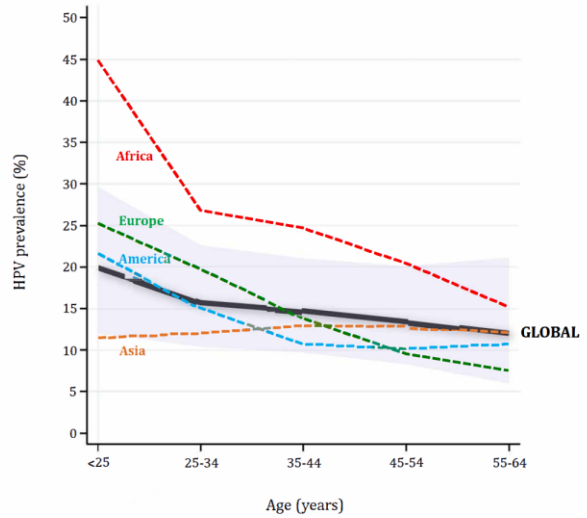

Voor elke oplossing
is wel een probleem.
Spreuktegeltje.nl

Noodzaak secundaire triage

- Partiële genotypering + cytology (ASCCP / Australië
- Cytology

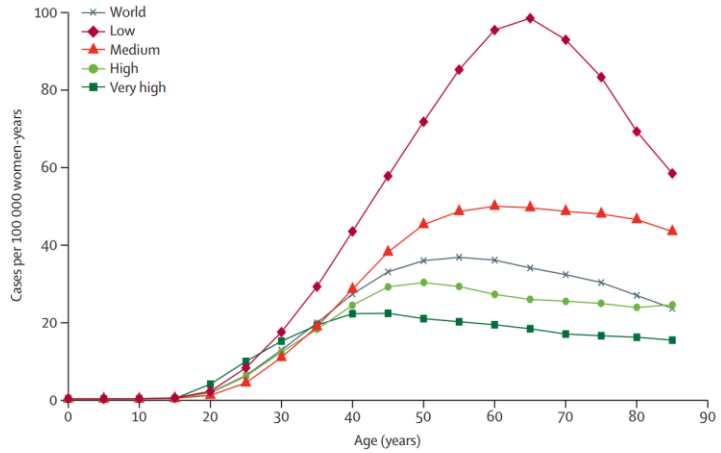
- P16/Ki67 dual stain
- Methylatie
- volledige genotypering

Fig. 1.8 Age-specific standardized prevalence of human papillomavirus (HPV) infection by world region



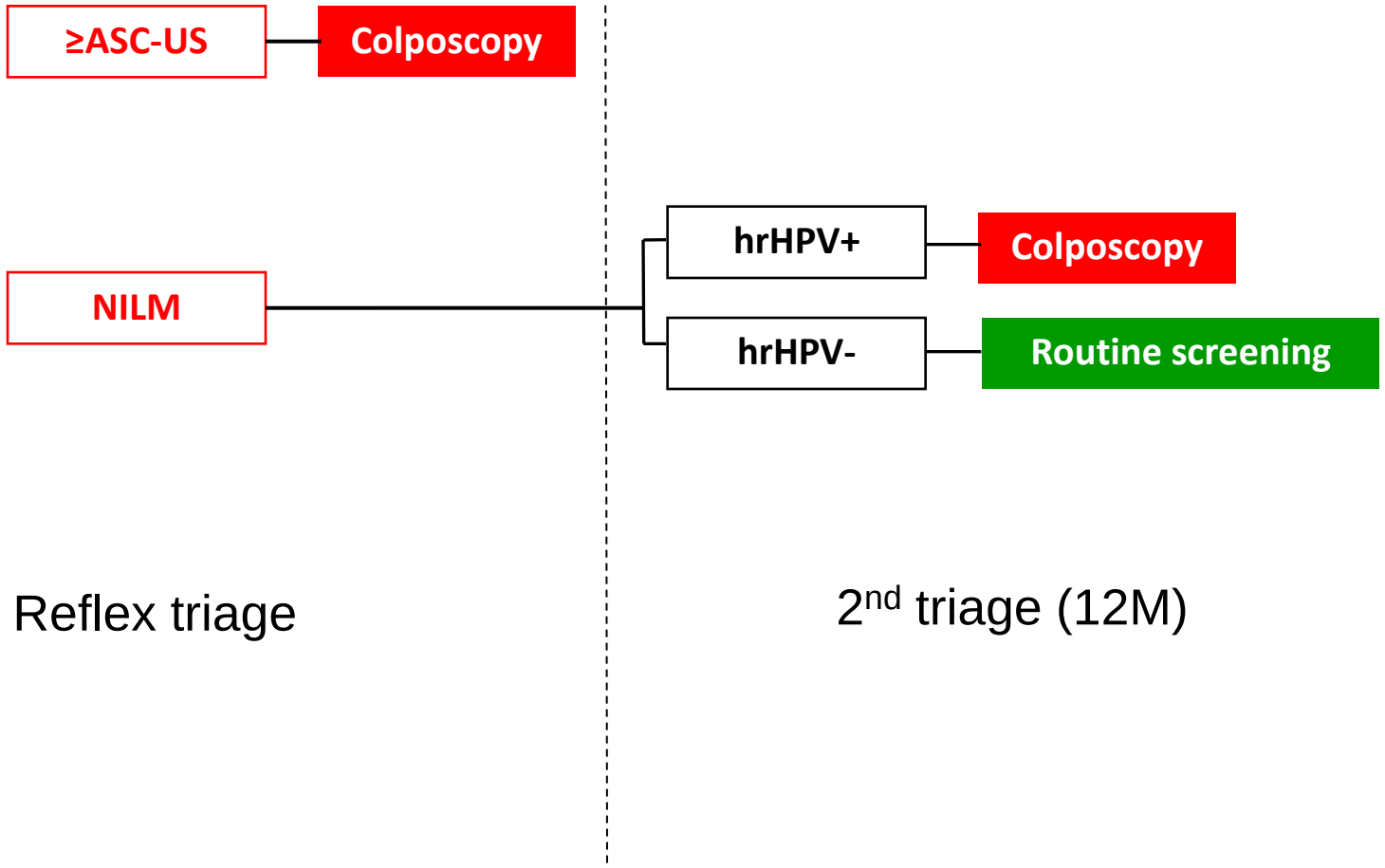
The shaded area represents the 95% confidence interval for the global HPV prevalence.
Courtesy of Laia Bruni, Bruni et al. (2016).

Fig. 1.4 Age-specific incidence of cervical cancer worldwide and in terms of the four-tier Human Development Index (HDI), 2018

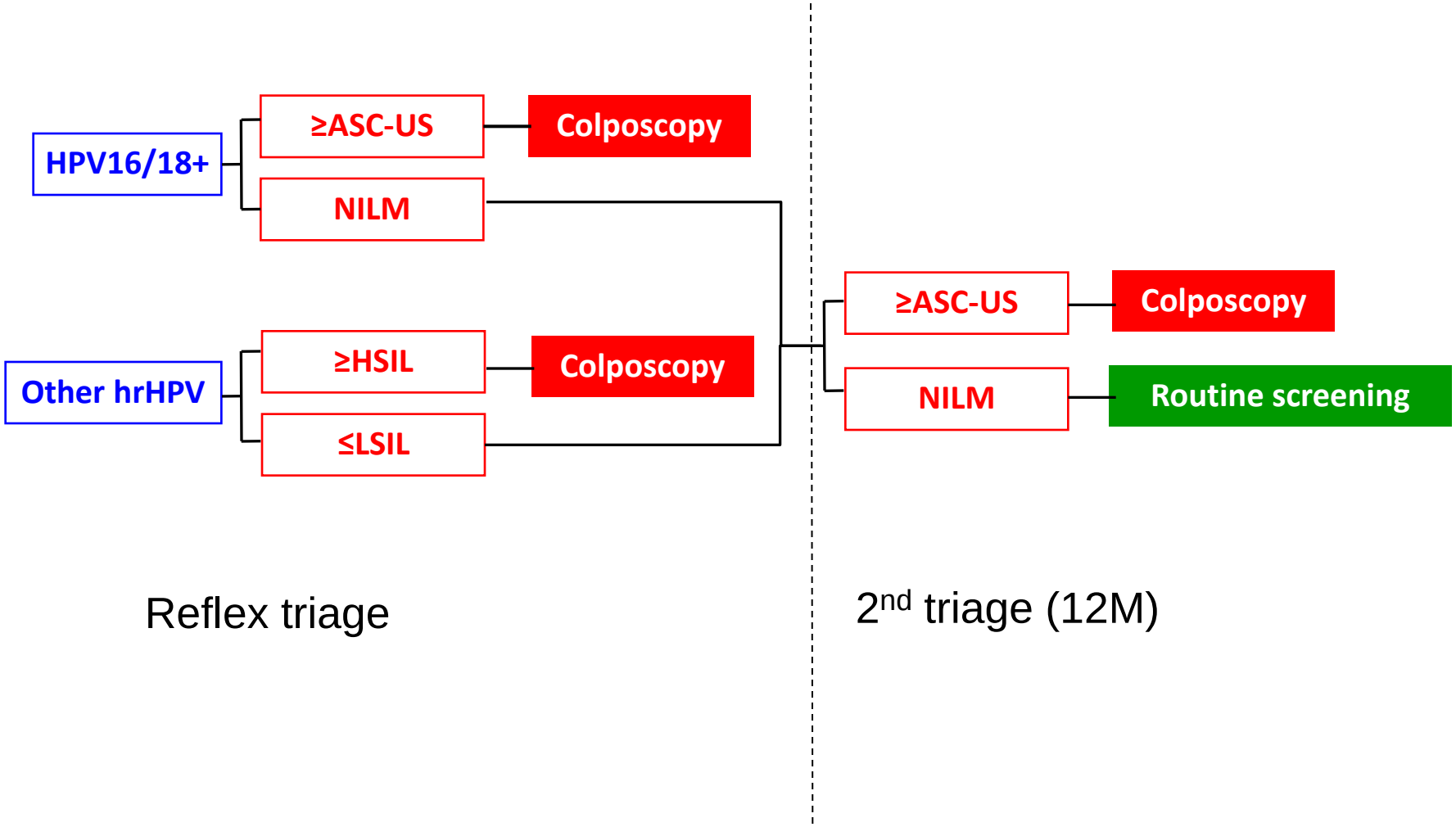


The four tiers of HDI are: low (< 0.55), medium (≥ 0.55 to < 0.7), high (≥ 0.7 to < 0.8), and very high (≥ 0.8).
Reproduced from Arbyn et al. (2020).

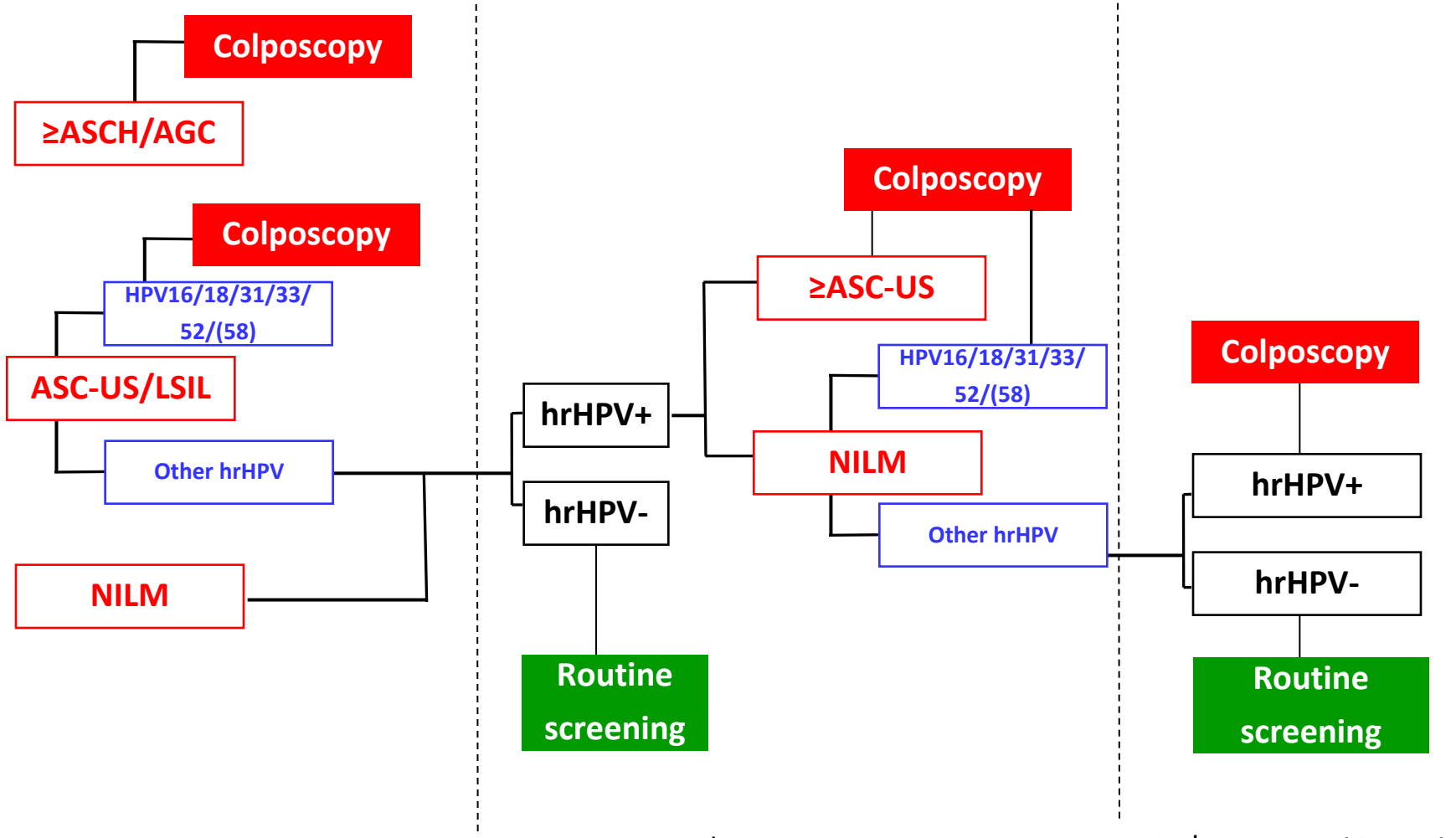
Triage of HPV+ women: FR, EI, IT, LT, MO, SC (Oct 2022-Jan 2023)



Triage of HPV+ women: NL (25 Oct, 2022)



Triage of HPV+ women: DK (22 Nov 2022)



CvKO
CENTRUM VOOR
KANKEROPSPORING

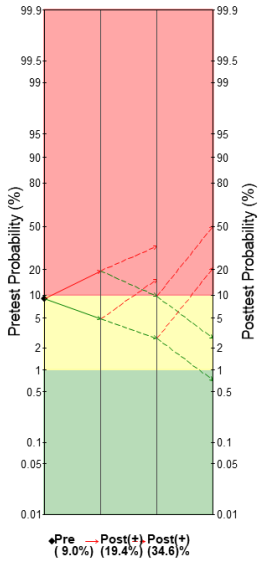
1 AUG 2023 – 18 SEP 2023

DOMUS
MEDICA

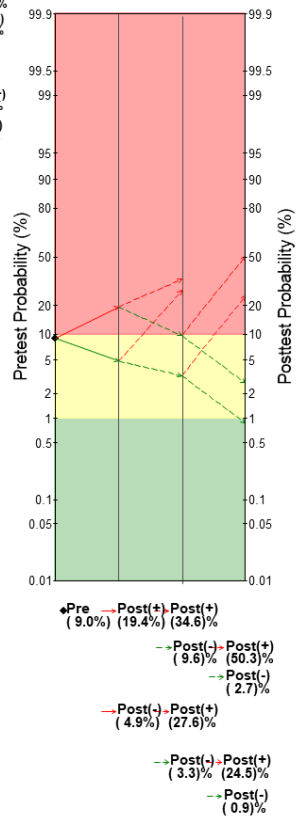
sciensano

Belgian Cancer Registry

Slide 3

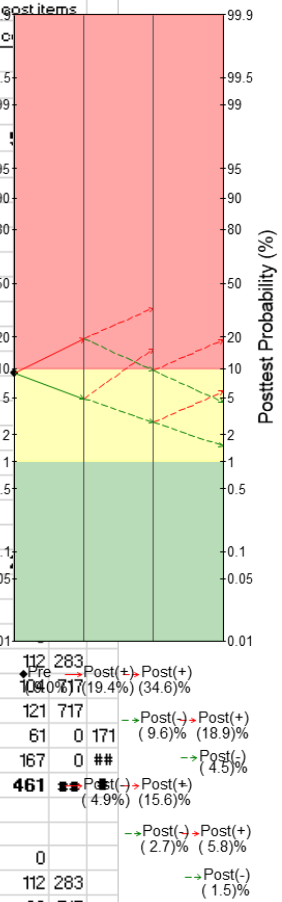


Slide 4

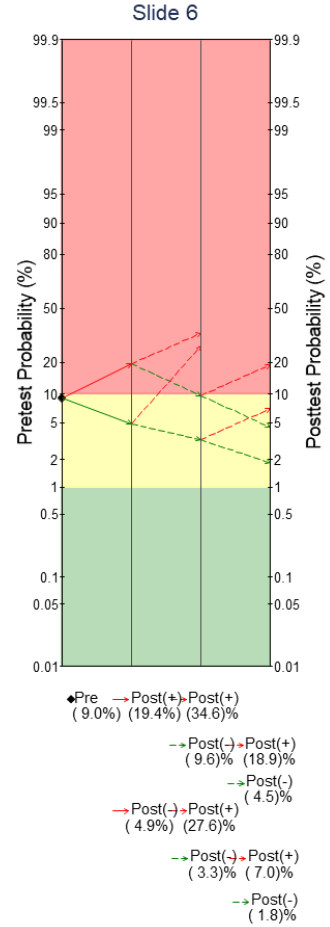


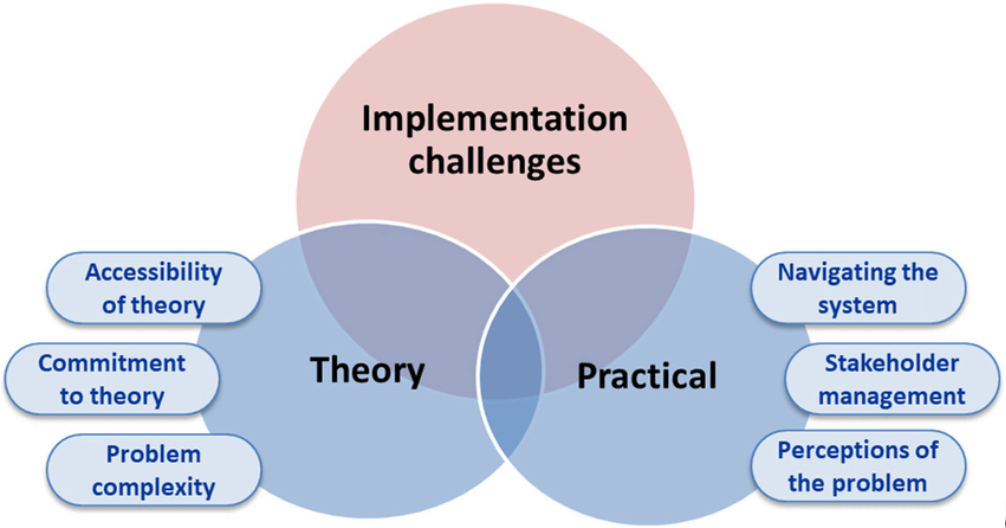
	A	B	C	D	E	F	G	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
1	slide 1			TirageMeeting1aug2023.pp			Nb				Useful referral	Missed	Unneces s refs	True re-assuranc										
2	Num		T1		T2	triage2	studies	sens	spec	prev	TP	FN	FP	TN	total	PPV	1/PPV	NPV	cNPV	%T+	ok	cost items		
3	24		H1618				15	0,61	0,75	####	55	35	228	683	###	##	5,15	0,95	###	###	yn			
4				oth:ASC-US+			7	0,6	0,7	####	20	15	184	499	718	##	10,20	0,97	###	###	yn			
5					oth,NILM: hr+		calc	0,8	0,9	####	11	4	42	457	514	##	4,82	0,99	###	0,10	yy			
6			**overall procedure**					**1**	###		**86**	**4**	**454**	**457**	##	**0**	6,28	**1**	###	**1**	**yy**			
12	slide 3																							
13	24		H1618				15	0,61	0,75	####	55	35	228	683	###	0,19	5,15	0,95	###	###	yn			
14		refla		H1618+>ASCUS+			11	0,70	0,68	####	39	16	73	155	283	##	2,87	0,91	###	###	yn			
15		reflb		oth>LSIL+			2	0,43	0,87	####	15	20	89	593	717	0,14	6,93	0,97	###	0,15	yn			
16						alternative	5	0,54	0,85	####	19	16	102	580	717	0,16	6,37	0,97	###	0,17	yn			
17	12m after	refla		H1618+>NILM>			calc	0,76	0,92	####	12	4	13	142	171	##	2,08	0,97	###	0,15	yn			
18	12m after	reflb		oth>ASCUS+			calc	0,76	0,92	####	12	4	49	531	596	##	5,08	0,99	###	0,10	yy			
19			**overall procedure**								**82**	**8**	**237**	**673**	##	##	**3,89**	###	###	##	**yn**			
20																								
21	slide 4																							
22	24		H1618				15	0,61	0,75	####	55	35	228	683	###	0,19	5,15	0,95	###	###	yn			
23		refla		H1618+>ASCUS+			11	0,70	0,68	####	39	16	73	155	283	##	2,87	0,91	###	###	yn			
24		reflb		oth>HSIL+			2	0,17	0,98	####	6	29	14	668	717	0,30	3,33	0,96	###	###	yn			
25						alternative	5	0,37	0,95	####	13	22	34	648	717	0,28	3,62	0,97	###	###	yn			
26	12m after	refla		H1618+>NILM>			calc	0,76	0,92	####	12	4	13	142	171	##	2,08	0,97	###	0,15	yn			
27	12m after	reflb		oth>LSIL->hr			calc	0,76	0,92	####	17	5	55	593	670	##	4,24	0,99	###	0,11	yy			
28			**overall procedure**								**81**	**9**	**175**	**735**	##	##	**3,16**	###	###	##	**yn**			
29																								
30	slide 5																							
31	24		H1618				15	0,61	0,75	####	55	35	228	683	###	0,19	5,15	0,95	###	###	yn			
32		refla		H1618+>ASCUS+			11	0,70	0,68	####	39	16	73	155	283	##	2,87	0,91	###	###	yn	112	283	
33		reflb		oth>LSIL+			2	0,43	0,87	####	15	20	89	593	717	0,14	6,93	0,97	###	0,15	yn	104	717	
34						alternative	5	0,54	0,85	####	19	16	102	580	717	0,16	6,37	0,97	###	0,17	yn	121	717	
35	12m after	refla		H1618+>NILM>ASC+			assu	0,70	0,68	####	11	5	50	105	171	##	5,55	0,95	###	###	yn	61	0	171
36	12m after	reflb		oth^ASC->ASC+			assu	0,60	0,7	####	10	6	157	423	596	##	16,70	0,99	###	###	nn	167	0	##
37			**overall procedure**								**79**	**11**	**382**	**528**	##	##	**5,84**	###	###	##	**yn**	**461**	##	#
38																								
39	slide 6																							
40	24		H1618				15	0,61	0,75	####	55	35	228	683	###	0,19	5,15	0,95	###	###	yn	0		
41		refla		H1618+>ASCUS+			11	0,70	0,68	####	39	16	73	155	283	##	2,87	0,91	###	###	yn	112	283	
42		reflb		oth>HSIL+			2	0,17	0,98	####	6	29	14	668	717	0,30	3,33	0,96	###	###	yn	20	717	
43						alternative	5	0,37	0,95	####	13	22	34	648	717	0,28	3,62	0,97	###	###	yn	47	717	
44	12m after	refla		H1618+>NILM>ASC+			calc	0,70	0,68	####	11	5	50	105	171	##	5,55	0,95	###	###	yn	61	0	171
45	12m after	reflb		oth^LSIL->ASC+			calc	0,60	0,73	####	13	9	175	473	670	##	14,46	0,98	###	###	yn	188	0	##
46			**overall procedure**								**76**	**14**	**332**	**578**	##	##	**5,37**	###	###	##	**yn**	**408**	##	#

Slide 5



Slide 6




Implementation challenges
Accessibility of theory
Commitment to theory
Problem complexity
Theory
Practical
Navigating the system
Stakeholder management
Perceptions of the problem


consens us

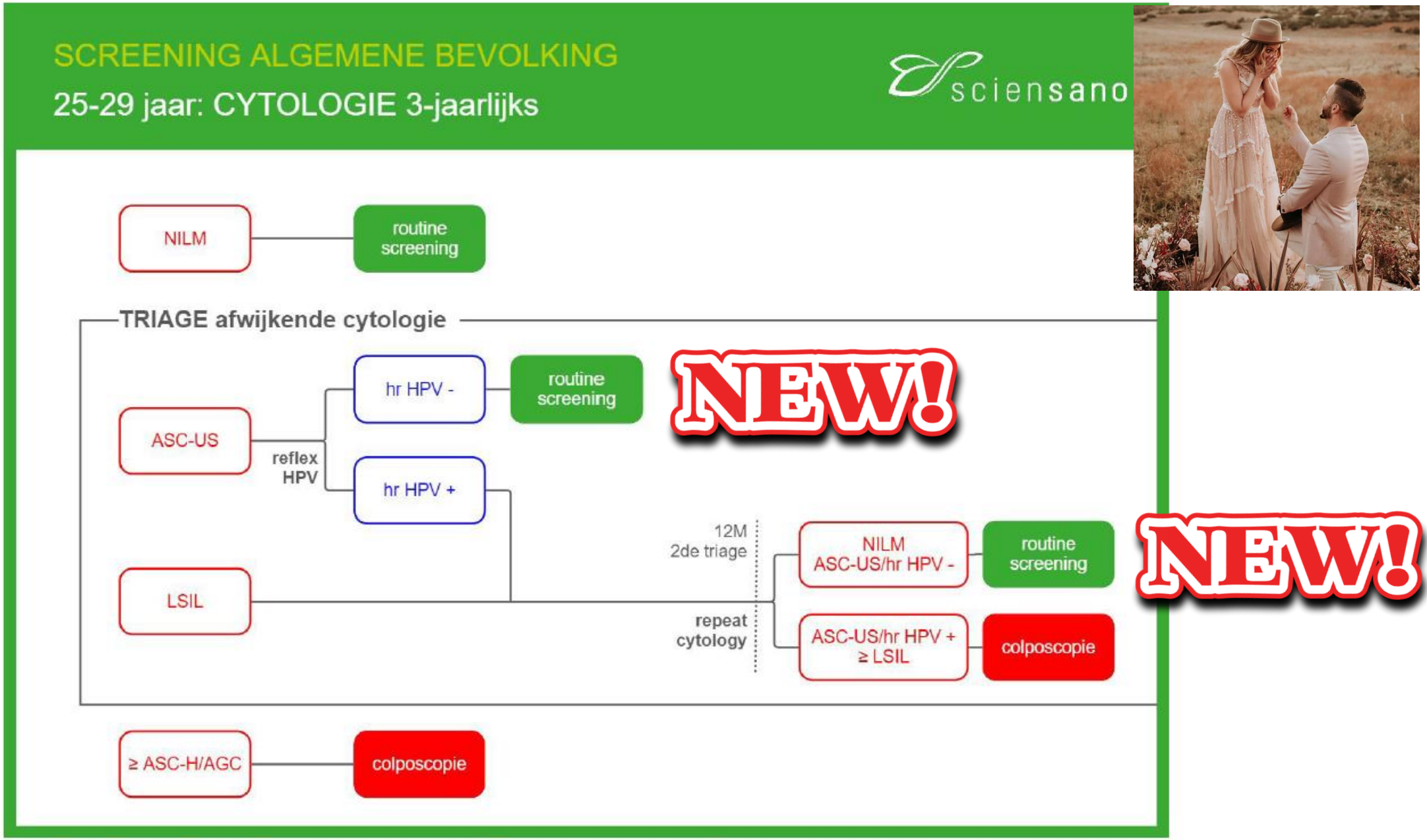

MEDIUM
LOW
HIGH
RISK?

Implementatie plan HPV Screening

01 01 2025

We're almost there !

FIGUUR 1: SCREENINGSALGORITME VOOR 25 TOT 29-JARIGEN IN DE ALGEMENE BEVOLKING (versie 1 – d.d. 20241015)



≥ASC-H/AGC = ASC-H/AGC of een hooggradigere afwijking (HSIL, SCC, AIS, AC)

Opgelet: Een ASC-US resultaat wordt altijd gevolgd door een reflex HPV-test (zowel bij de primaire screening als bij de 2de triage na 12 maanden)

FIGUUR 2: SCREENINGSALGORITME VOOR 30 TOT 64-JARIGEN IN DE ALGEMENE BEVOLKING (versie 1 - d.d. 20241015)

SCREENING ALGEMENE BEVOLKING

30-64 jaar: HPV-test 5-jaarlijks

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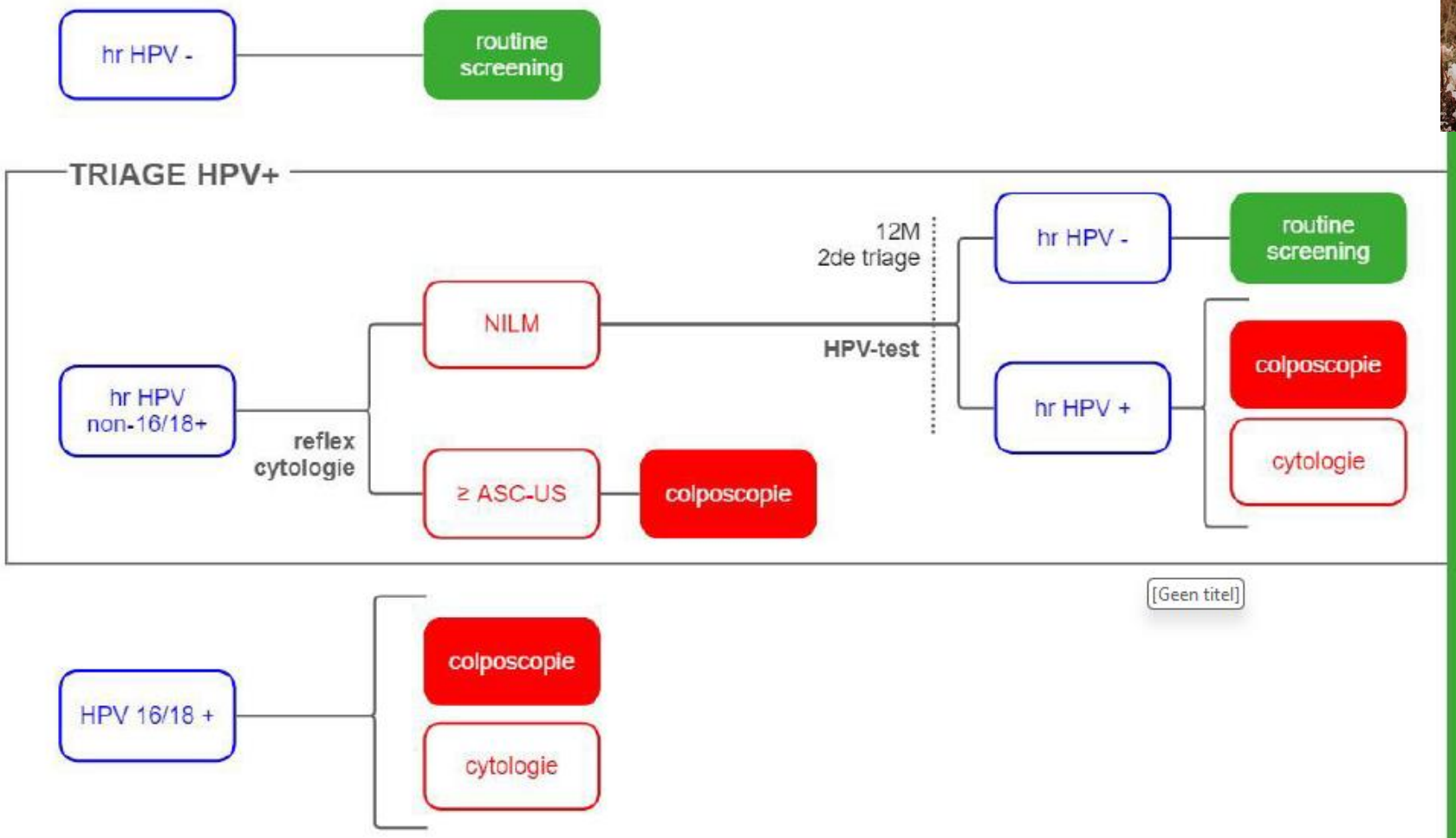


Opgelet: Een positief hrHPV-resultaat wordt altijd gevolgd door een reflex cytologie (zowel bij de primaire screening als bij de 2de triage na 12 maanden)

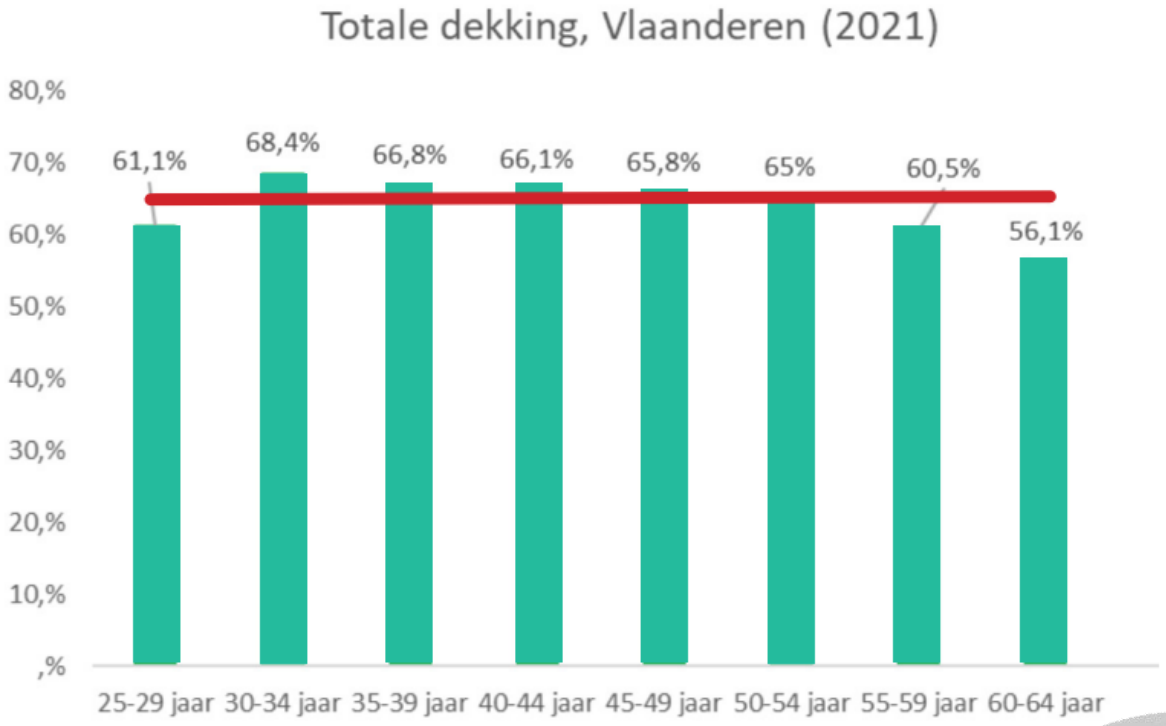
sciensano

KANKERCENTRUM

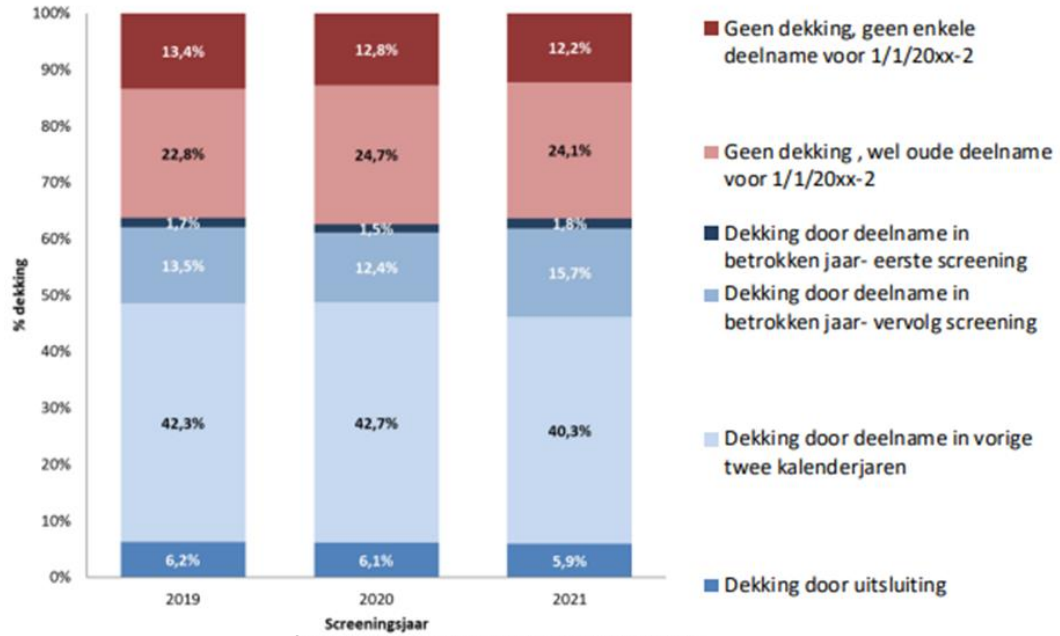
INTRODUCTIE VAN DE HPV-TEST IN BAARMOEDERHALSKANKER SCREENING IN BELGIË


THE
ThinPrep
PAP TEST

Opportuniteiten



Figuur 1: Evolutie van de totale dekking met opsplitsing op basis van de meest recente deelname.



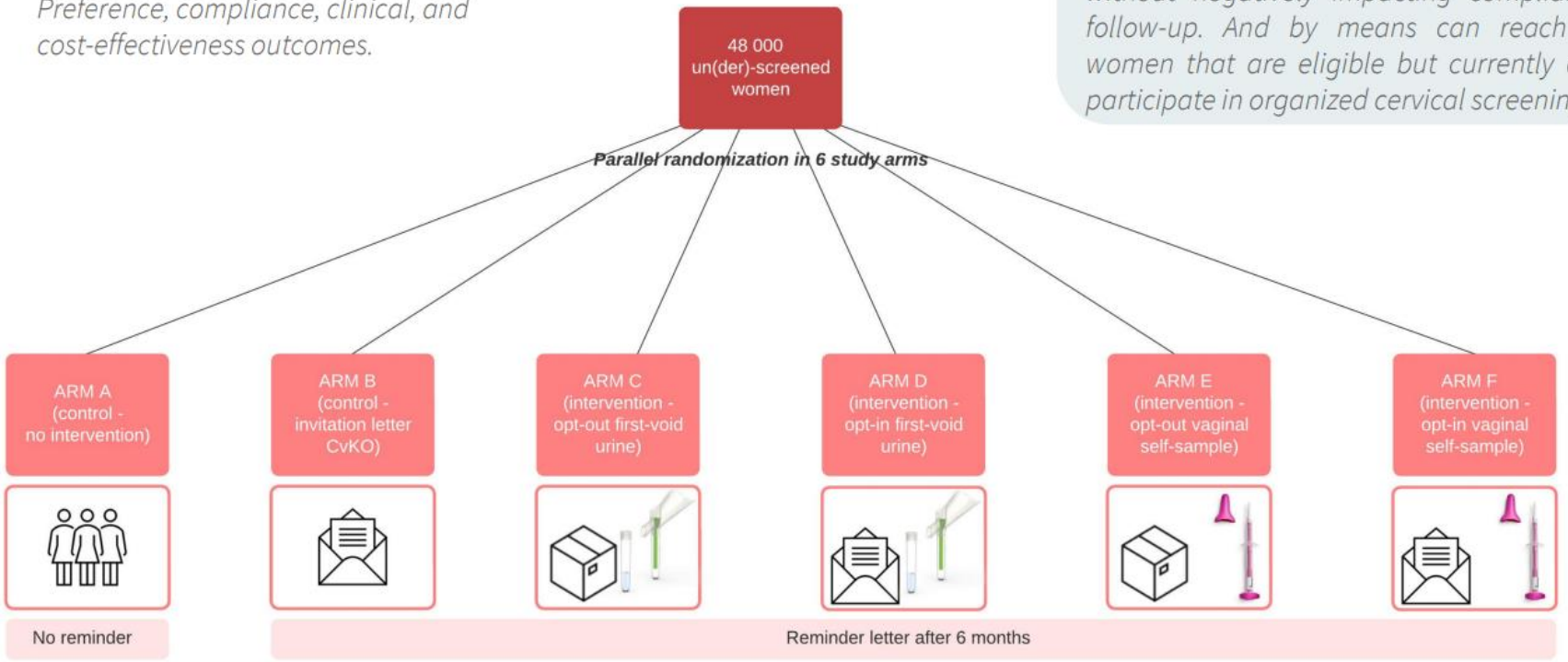
JAARRAPPORT BEVOLKINGSONDERZOEK.BE

Opportunities

ScreenUrSelf

Preference, compliance, clinical, and cost-effectiveness outcomes.

*Verification of the **primary study hypothesis** that a hrHPV test on a home collected **first-void urine sample is more preferred by un(der)-screened women** than vaginal self-sampling is, without negatively impacting compliance to follow-up. And by means can reach more women that are eligible but currently do not participate in organized cervical screening.*



Un(der)-screened women: No cytological, histological, pathological reports in Belgian Cancer Register for ≥2 screening rounds (30-64y), residing in Flanders, not included in other CvKO research projects, no history of total hysterectomy nor uterine/cervical cancer, and not actively opted out of the organized screening program.

Lancet Oncol 2022; 23: 950–60
Published Online
June 13, 2022
https://doi.org/10.1016/
S1470-2045(22)00294-7

Accuracy and effectiveness of HPV mRNA testing in cervical cancer screening: a systematic review and meta-analysis

Marc Arbyn, Marie Simon, Silvia de Sanjosé, Megan A Clarke, Mario Poljak, Remila Rezhake, Johannes Berkhof, Victoria Nyaga, Murat Gultekin, Karen Canfell, Nicolas Wentzensen

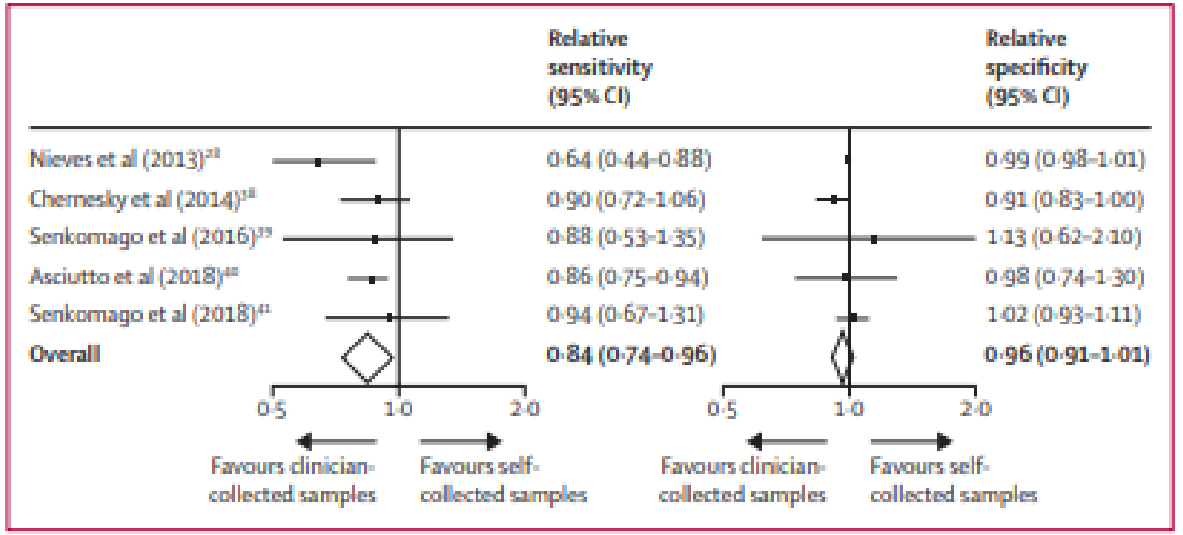


Figure 2: **Relative sensitivity and specificity of high-risk human papillomavirus mRNA testing to detect CIN2+ on vaginal self-collected cervical specimens versus clinician-collected cervical specimens**
The pooled relative accuracy estimate is shown as a diamond, with its width representing the 95% CI.
CIN2+=cervical intraepithelial neoplasia of grade 2 or worse.

Het laboratorium dat de primaire screeningtest heeft uitgevoerd, stelt een geïntegreerd advies op.

De resultaten van de reflextest worden overgemaakt aan de zorgverlener die de primaire screeningstest heeft uitgevoerd. Op basis van beide resultaten verstrekt het primaire laboratorium een advies betreffende de verder te volgen therapeutische houding (= geïntegreerd advies) aan de aanvragende arts en – in de toekomst – aan het Belgian Cancer Registry (BCR).

- **TABEL 2: GEÏNTEGREERD ADVIES – 25-29 EN 30-64 JARIGEN**

Leeftijdscategorie: 25-29 jaar					
Resultaat cytologisch onderzoek	**Resultaat reflex hrHPV test**	**(Geïntegreerd) advies**	**Resultaat 2de triage (over 12 maanden)**	**Resultaat reflex hrHPV test**	**(Geïntegreerd) advies**
NILM	nvt	Normaal herhalingsschema (over 3 kalenderjaren)			
ASC-US		**Resultaat reflex HPV-test, met advies, volgt**			
	--> negatief voor hrHPV	**Normaal herhalingsschema (over 3 kalenderjaren)**			
	--> positief voor hrHPV	**Herhaal cytologie over 12 maanden**	--> NILM	nvt	Normaal herhalingsschema (over 3 kalenderjaren)
			--> ASC-US		**Resultaat reflex HPV-test, met advies, volgt**
				--> negatief voor hrHPV	**Normaal herhalingsschema (over 3 kalenderjaren)**
				--> positief voor hrHPV	**Directe verwijzing voor colposcopisch onderzoek**
			--> ≥ LSIL		Directe verwijzing voor colposcopisch onderzoek
LSIL	nvt	Herhaal cytologie over 12 maanden	--> NILM	nvt	Normaal herhalingsschema (over 3 kalenderjaren)
			--> ASC-US		**Resultaat reflex HPV-test, met advies, volgt**
				--> negatief voor hrHPV	**Normaal herhalingsschema (over 3 kalenderjaren)**
				--> positief voor hrHPV	**Directe verwijzing voor colposcopisch onderzoek**
			--> ≥ LSIL		Directe verwijzing voor colposcopisch onderzoek
≥ ASC-H/AGC	nvt	Directe verwijzing voor colposcopisch onderzoek		nvt	
INSU	nvt	Nieuwe staalname ten vroegste binnen 6 weken		nvt	

Leeftijdscategorie: 30-64 jaar					
Resultaat hrHPV test	**Resultaat reflex cytologie**	**(Geïntegreerd) advies**	**Resultaat 2de triage (over 12 maanden)**	**(Resultaat reflex cytologie)**	**Advies**
Negatief voor hrHPV	nvt	Normaal herhalingsschema (over 5 kalenderjaren)			
Positief voor hrHPV niet-16/18		**Resultaat reflexcytologie, met advies, volgt**			
	--> ≥ ASC-US	**Directe verwijzing voor colposcopisch onderzoek**			
	--> NILM	**Herhaal hrHPV-test over 12 maanden**	--> negatief voor hrHPV		Normaal herhalingsschema (over 5 kalenderjaren)
			--> positief voor hrHPV	(cytologie, niet als triage)	Directe verwijzing voor colposcopisch onderzoek
					Resultaat reflexcytologie volgt
Positief voor HPV 16/18	(cytologie, niet als triage)	Directe verwijzing voor colposcopisch onderzoek			
		Resultaat reflexcytologie volgt			
HPVi		Nieuwe staalname ten vroegste binnen 6 weken			

≥ASC-H/AGC = ASC-H/AGC of een hooggradigere afwijking (HSIL, SCC, AIS, AC)

BELAC

- BELAC
  - ISO 15189-accreditatie voor art 24bis
  - HPV test uit NRC-HPV lijst
- Registratie
  - Labo ➔ BCR (art 5a van art. 24 bis)
  - Gestructureerd (HL7-FHIR)

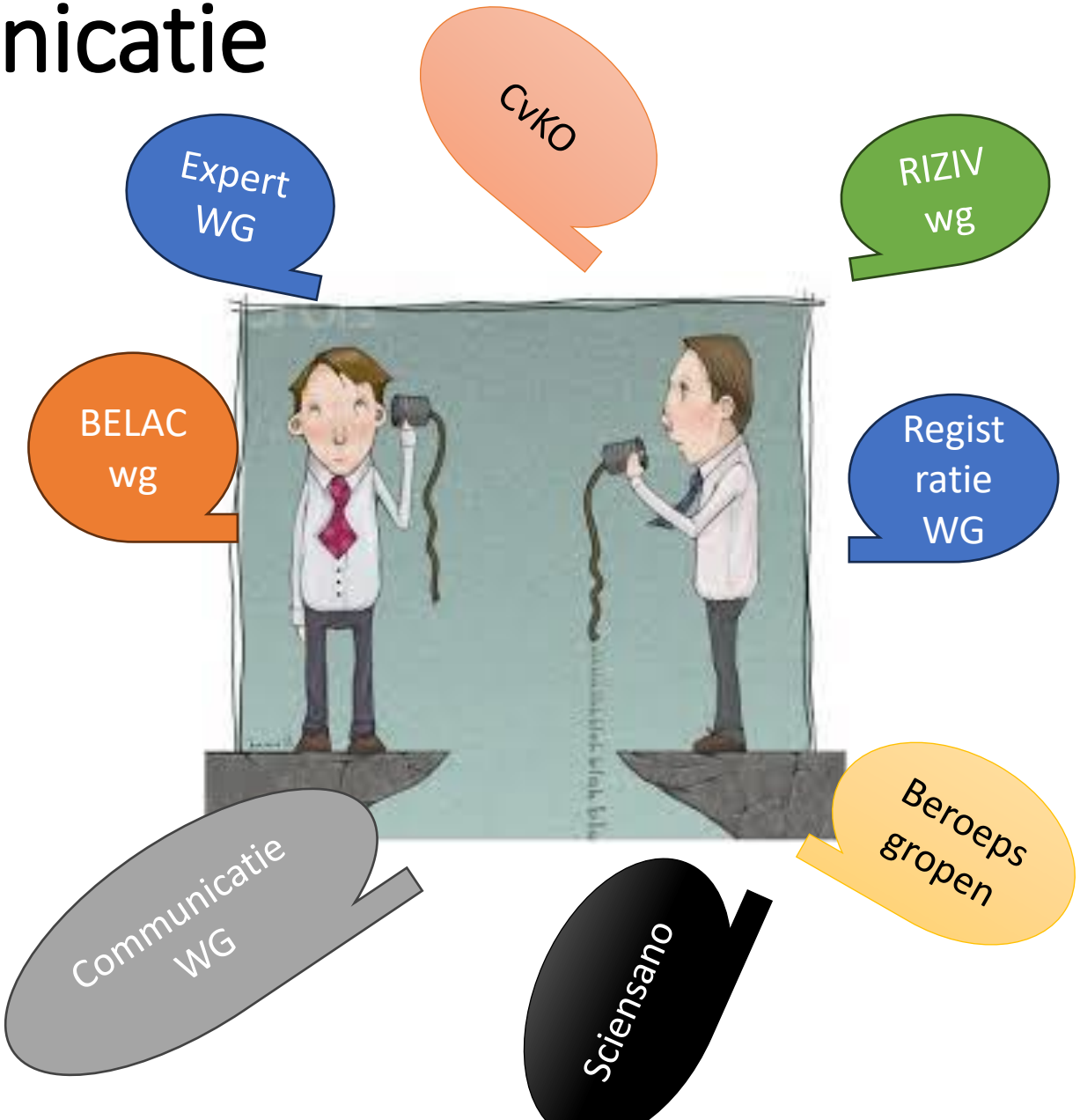
Communicatie

Linger

(verb)

[Geen titel]

remain at a place longer than necessary; hang around




Focus On The Goal


EUROPE'S BEATING CANCER PLAN
LET'S STRIVE FOR MORE
#EUCancerPlan
4 February 2020, European Parliament, Brussels


Reaching the 2030 targets for cervical cancer elimination:
New WHO recommendations for screening and treatment