Cervical cancer screening: Signposts for a Changing World

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Belgian Week of Pathology

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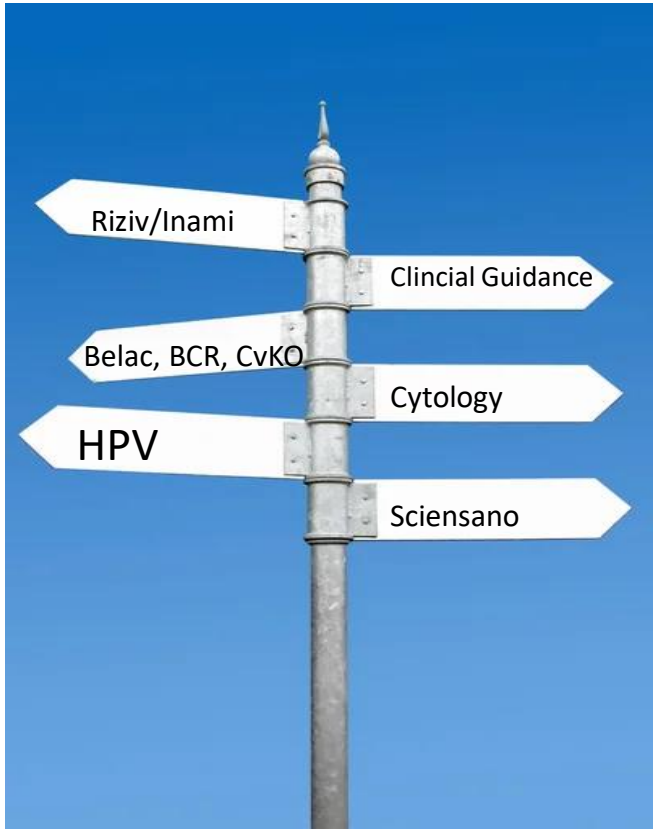


1/1/2025: introduction of primary HPV screening in Belgium

- The new screening algorithm
- Reimbursement rules (Riziv/Inami)
- Clinical Guidance (Sciensano)

New screening algorithm (general remarks)

- Age: “the calendar year in which one turns X years old”
- Setting
  - Primary screening
  - Follow-up (diagnostic or therapeutic)
  - Clinical testing (symptoms)
  - High-risk populations
- Misalignment clinical guidance (Sciensano) and RIZIV/INAMI rules
- Integrated advice: to be provided by the lab performing the 1st test (HPV or cytology)
- Self sampling: to be introduced by the Regions

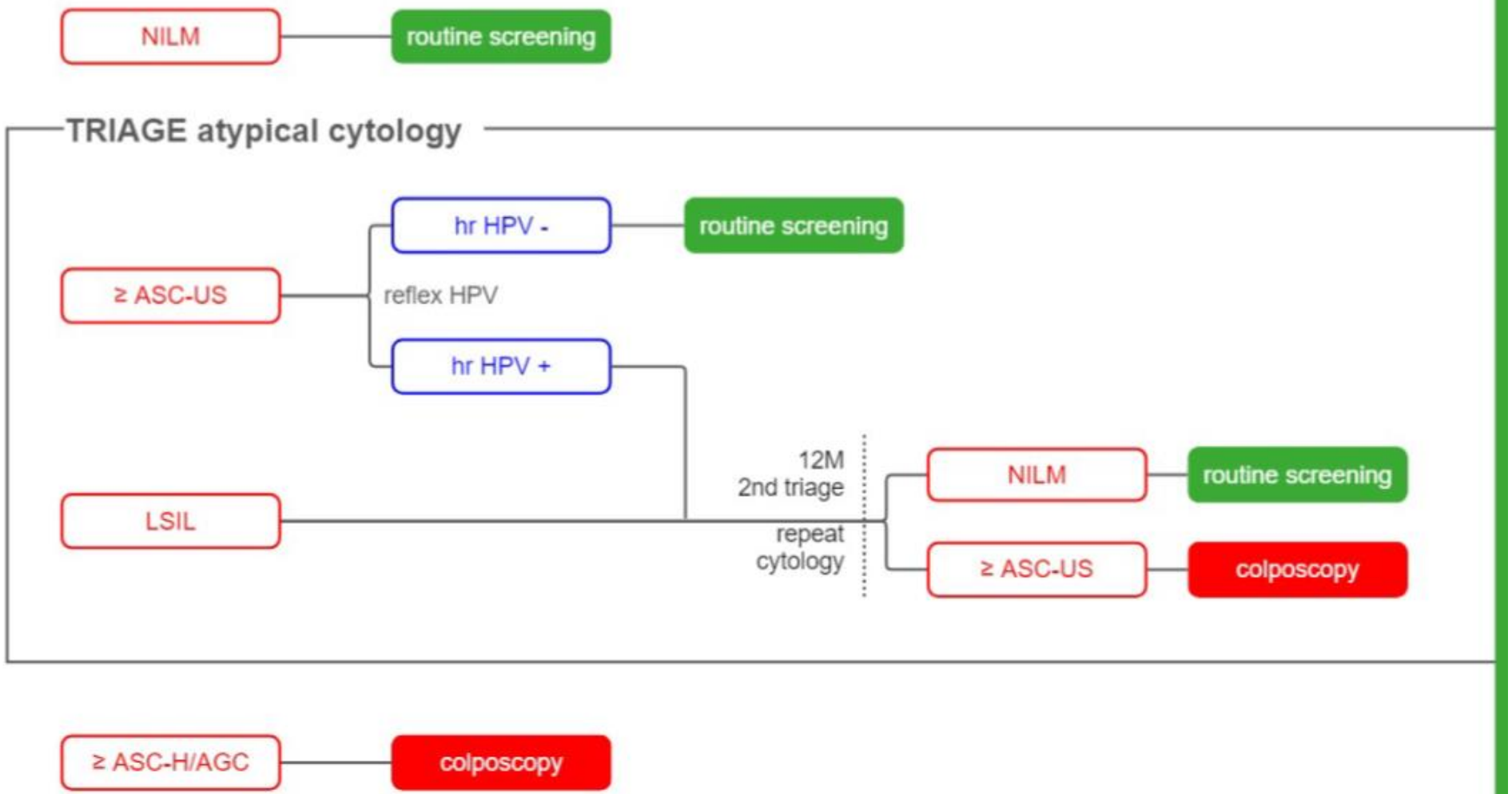
Screening

Follow-up

SCREENING OF THE GENERAL POPULATION

25-29 years: CYTOLOGY 3-yearly

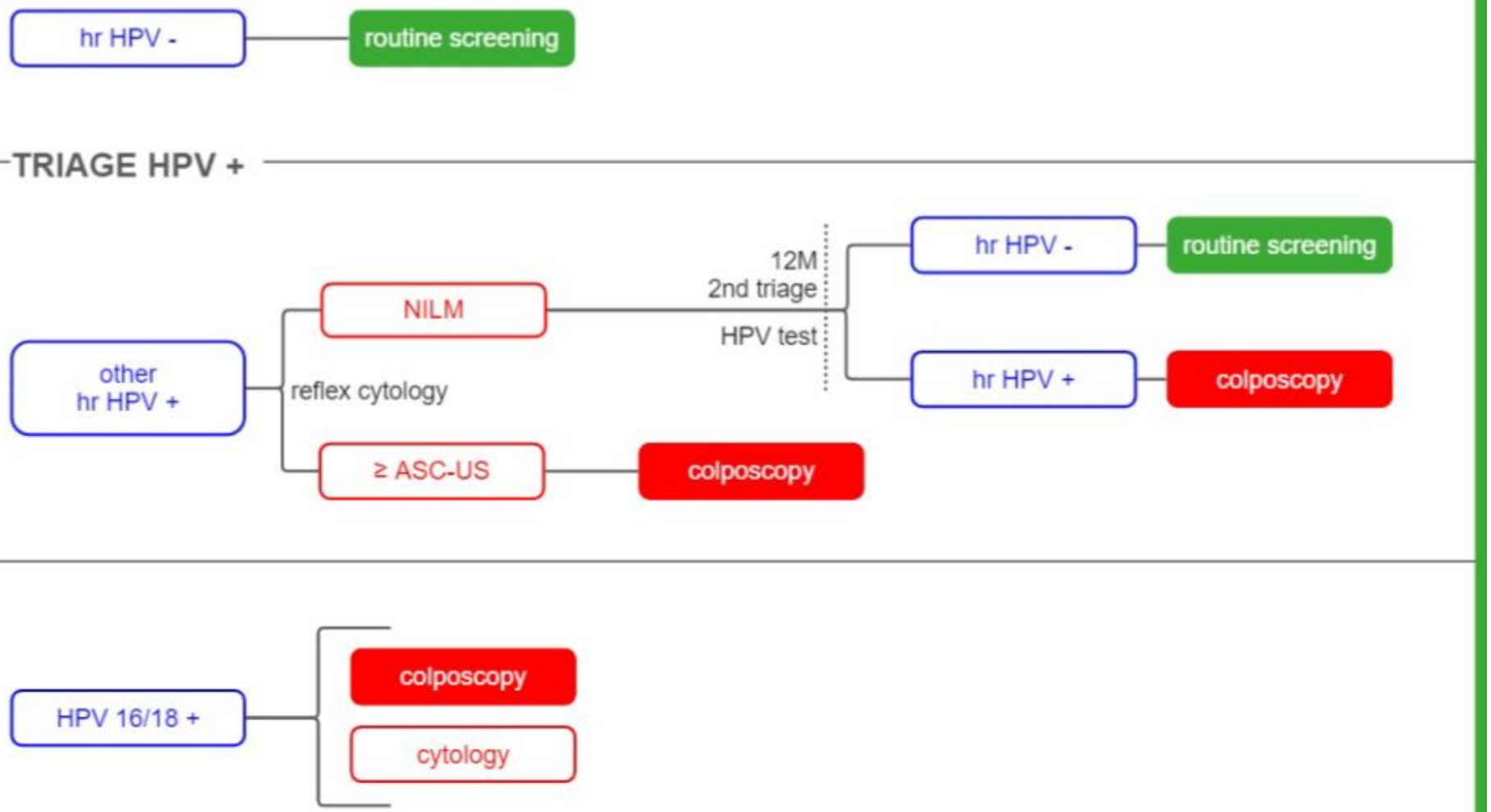
sciensano



SCREENING OF THE GENERAL POPULATION

30-64 years: HPV test 5-yearly

sciensano



Integrated advice:

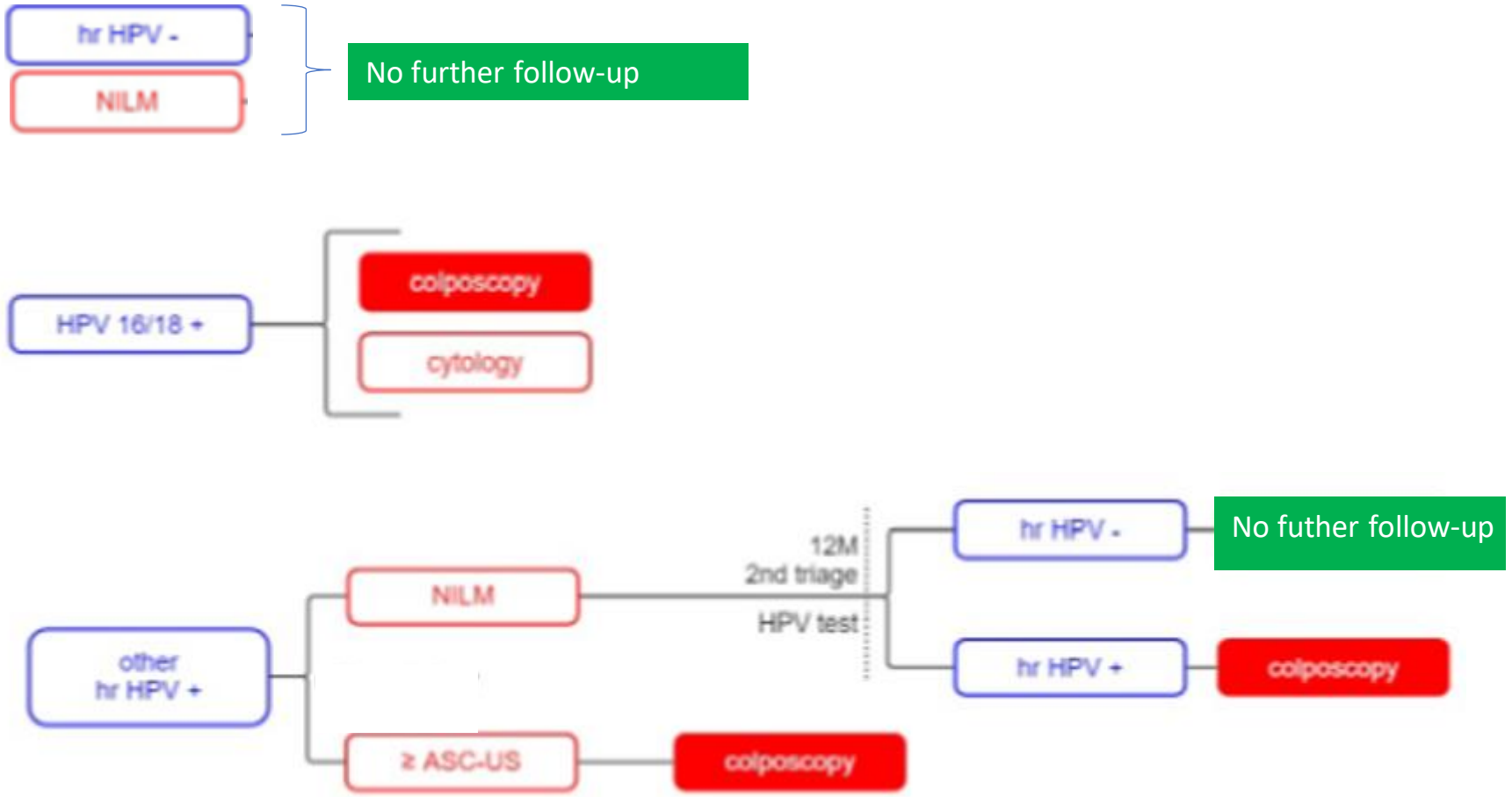
Age range: 25-29 years		
Result cytological examination	**Result reflex hrHPV test**	**Integrated advice**
NILM	NA	Regular screening interval (in 3 calendar years)
ASC-US		Result of reflex HPV test with recommendation will follow
	--> hrHPV negative	Regular screening interval (in 3 calendar years)
	--> hrHPV positive	Repeat cytology in 12 months
LSIL	NA	Repeat cytology in 12 months
≥ ASC-H/AGC	NA	Immediate referral for colposcopic examination
INSU	NA	New sampling after 6 weeks at the earliest

Integrated advice:

Age range: 30-64 years		
Result hrHPV test	**Result reflex cytology**	**Integrated advice**
hrHPV negative	NA	Regular screening interval (in 5 calendar years)
HPV 16/18 positive		Immediate referral for colposcopic examination. Result of reflex cytology will follow
hrHPV non-16/18 positive		Result of reflex cytology with recommendation will follow
	--> cytology ≥ ASC-US	Immediate referral for colposcopic examination
	--> cytology NILM	Repeat hrHPV testing in 12 months
HPVi		New sampling after 6 weeks at the earliest

SCREENING OF THE GENERAL POPULATION

≥65 years: one-time (catch-up) cytology and HPV co-test*



* If no screening (cytology or HPV) has been reimbursed in the last 10 years

Screening in ‘special’ cases (exceptions)

Clinical/Diagnostic	guideline	reimbursement	
	Cotesting (cytology + HPV)	One diagnostic co-test	Notification by physician*
Uterine blood loss (postmenopausal, abnormal therapy-resistant, unexplained postcoital)			

*a notification form by the physician → insurance company of the patient

Screening in ‘special’ cases (exceptions)

Hig-Risk groups	guideline	reimbursement	
DES AIS	Cotesting (cytology + HPV)	No limitation	Notification by physician
Immunocompromised*	Cotesting (cytology + HPV)	No limitation Recommendation: 1x/year	Notification by physician

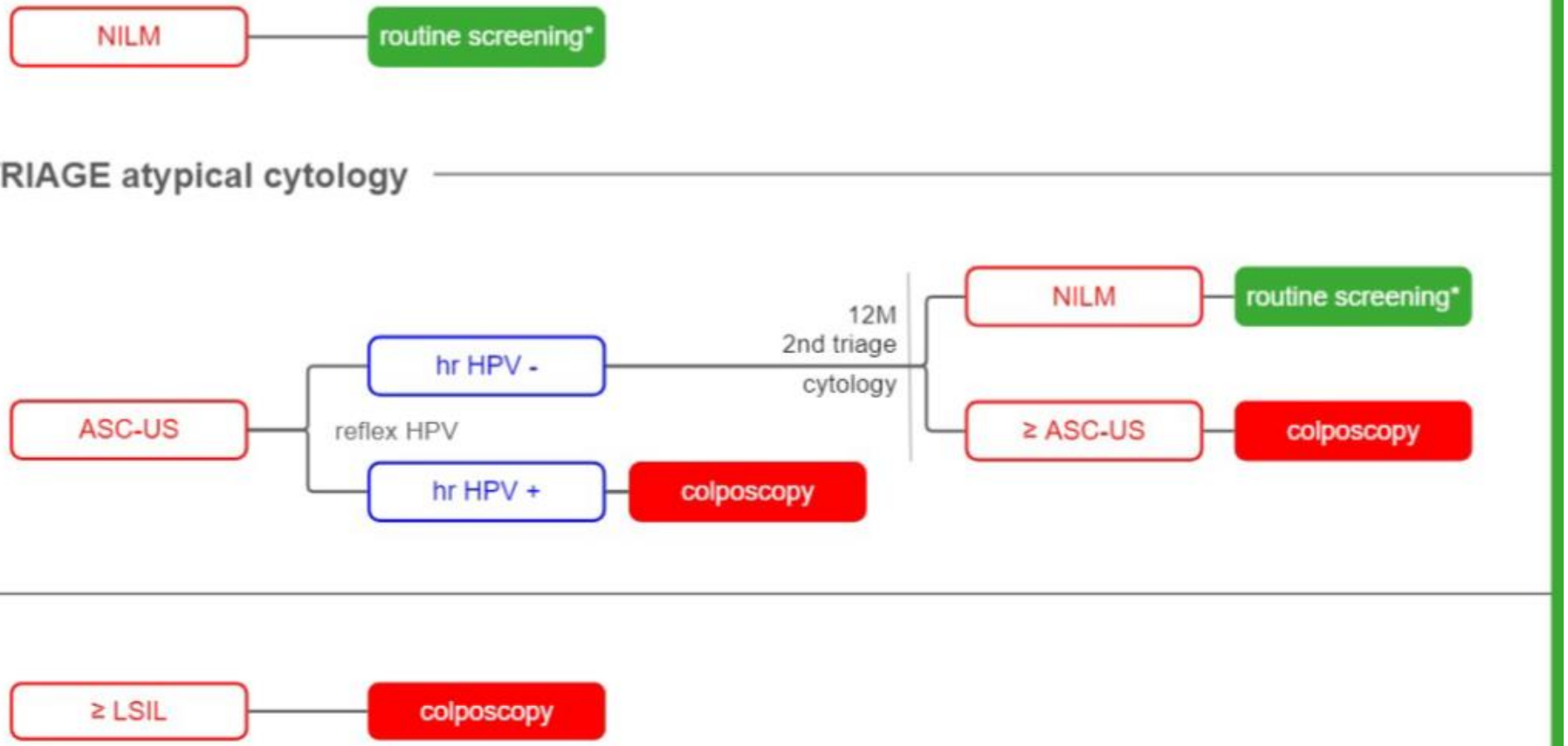
*Immunocompromised: HIV, organ transplant, ASCT, SLE, congenital PID, long-term immunosuppressants (MTX…)

Note: if HIV well controlled: normal screening interval!

SCREENING IMMUNOCOMPROMISED POPULATION

21-29 years: CYTOLOGY annually

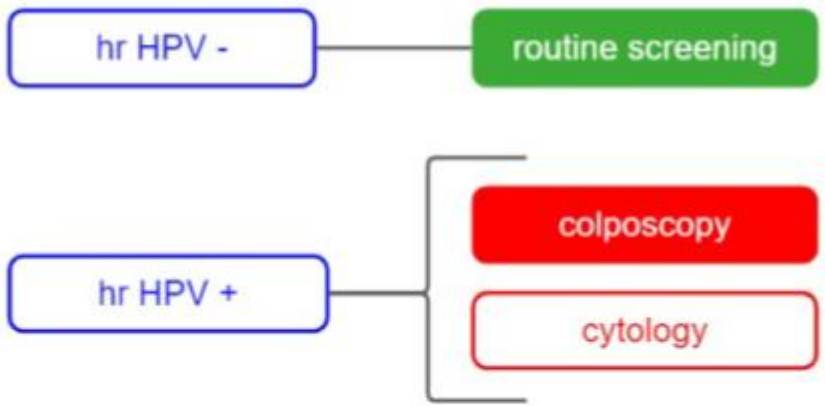
sciensano



*Systematic screening every 3 years if HIV is well controlled (CD4 ≥ 350/µL + HIV-RNA < 200cp/ml, for more than one year).

SCREENING IMMUNOCOMPROMISED POPULATION Δ

≥30 years: HPV test 3-yearly



Δ if HIV is well controlled (CD4≥350/µL+ HIV-RNA<200cp/ml, for more than one year)
→ see General population screening : 30-64 years: HPV test 5-yearly

Follow-up

Screening

Follow-up

	guideline	reimbursement	
Diagnostic or therapeutic follow-up*	Cytology and/or HPV-test	HPV 1x/year Cytology 1x/year	**
'Temporary high-risk' (e.g. untreated HSIL)	Cytology and/or HPV-test	HPV 2x/year Cytology 2x/year	Notification by physician

*no further specification in clinical guideline (sciensano) or RIZIV/INAMI
**No need for notification form in diagnostic/therapeutic follow-up

Reimbursement* allows for co-testing in:

- Diagnostic/therapeutic follow-up
- ‘Temporary high-risk’ (e.g. ‘untreated HSIL’)
- 65+ ‘catch-up’
- ‘high-risk patients’ (DES, AIS, immunocompromised)

*In conflict with Clinical Guideline (Sciensano) which advices against co-testing: ‘Please adhere to the above screening algorithms, even if the RIZIV/INAMI nomenclature allows broader testing possibilities’

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Co-testing: integrated advice? 65+

Clinical guideline: ‘for advice of cotest results, physicians are referred to the table underneath’:

ADVICE: ≥65y, in case of no reimbursed screening in the last 10 years

Age range: ≥ 65 year, in case of no screening in the last 10 years			
Result hrHPV test and cytology within cotesting	**Advice**	**Result repeat HPV testing**	**Advice**
HPV 16/18 positive, independant of cytology result	Immediate referral for colposcopic examination		
hrHPV non-16/18 positive	Result of reflex cytology with recommendation will follow		
--> cytology ≥ ASC-US	Immediate referral for colposcopic examination		
--> cytology NILM	Repeat hrHPV testing in 12 months	-> hrHPV negative	No further follow-up?
		-> hrHPV positive	Immediate referral for colposcopic examination?
hrHPV negative	Result of reflex cytology with recommendation will follow		
-> cytology ≥LSIL	Immediate referral for colposcopic examination		
-> cytology ASC-US	Repeat hrHPV testing in 12 months	-> hrHPV negative	No further folow-up
		-> hrHPV positive	Immediate referral for colposcopic examination?
-> cytology NILM	No further follow-up		

Co-testing: integrated advice (30-64 yr)

Clinical guideline* (Sciensano): ‘special indication, only during transition fase’ in case of previous co-testing

- hrHPV- ASCUS → routine screening
- hrHPV- LSIL → retest with HPV in 12 mths
  - hrHPV- → routine screening
  - hrHPV+ → colposcopy

Transition phase (according to Clinical Guideline/Sciensano)

According to the RIZIV/INAMI nomenclature, all insured people aged between 30 and 64 will enter the new system three years after the last reimbursed test for cervical cancer screening, regardless of whether they received a cytology or an HPV test in the past. They will at that point be entitled to a reimbursed HPV test that will be repeated every five years from that moment on.

Although nomenclature allows an HPV test for each woman 30-64 years old after 3 years, regardless of the previous test (cytology or HPV), the experts want to take previous HPV test results into account (any HPV test, even if it was an HPV test not on the list of acceptable test for the Belgian screening program). This means that women with a previous negative reflex HPV test result or a not-reimbursed negative HPV test result should only be advised for the next screening round in 5 years time.

Request form

INDICATIE VAN HET ONDERZOEK :

- ❑ BINNEN de georganiseerde screening naar baarmoederhalskanker
  - ❑ Van 25-29 j : primair cytologisch onderzoek met reflex HPV-testing als atypische cellen (1 x om de 3 kalenderjaren)
  - ❑ Van 30-64 j : primaire HPV-testing met reflex cytologie bij aanwezigheid van hr-HPV (1 x om de 5 kalenderjaren)
  - ❑ ≥ 65 j : éénmalig HPV- en/of cytologische test indien geen terugbetaalde screening in de voorbije 10 jaar

- ❑ Diagnostische of therapeutische opvolging, rekening houdend met de richtlijnen * (1x per kalenderjaar zolang medisch noodzakelijk)

  Motivatie : ……

  ❑ Cytologisch onderzoek ❑ HPV-testing ❑ co-testing

- ❑ Screening bij hoogrisico patiënt : klinisch/diagnostisch, hoogrisicogroep, tijdelijk hoogrisico.

  (notificatie aan adviserend arts van VI met indicatiestelling is verplicht en dient ingevuld te worden op de achterzijde van dit formulier**)

- ❑ BUITEN de georganiseerde screening : geen van bovenstaande indicaties (bv. < 25j, > 65j, andere……)

  (Indien HPV-bepaling : opleg € 30. De aanvrager bevestigt hierbij dat de patiënt hiervan op de hoogte werd gebracht.)

  ❑ Cytologisch onderzoek ❑ HPV-testing ❑ co-testing

Notification form

Standaardformulier ter notificatie van het gebruik van gereserveerde nomenclatuurcodes van artikel 24bis en artikel 32 van de nomenclatuur van de geneeskundige verstrekkingen in het kader van de screening naar baarmoederhalskanker

Op te sturen naar de adviserend arts van de verzekeringsinstelling

Identificatie van de rechthebbende :

Naam: ..... Voornaam: .....

Geboortedatum: .....

Adres: ..... Nr Ziekenfonds: .....

Indicatie waarvoor de notificatie wordt gemeld:

KLINISCH/DIAGNOSTISCH

Pseudocode	Indicatie	indicatie aanvinken	Nomenclatuurcode waarvan het gebruik wordt gemeld
A1H1	postmenopauzaal bloedverlies		A6H6 A9H9
A2H2	abnormaal therapieresistent uterien bloedverlies		A6H6 A9H9
A3H3	onverklaard postcoitaal bloedverlies		A6H6 A9H9

In het kader van de geattesteerde klinische episode wordt het recht op terugbetaling van één HPV-test en één cytologie-onderzoek toegestaan.

HOOGRISICOGROEPEN

Pseudocode	Indicatie	indicatie aanvinken	Nomenclatuurcode waarvan het gebruik wordt gemeld
A4H4	Immuungecompromitteerde patiënten[1]		A6H6 A9H9
A5H5	DES-slachtoffers		A6H6 A9H9
A6H6	Adenocarcinoma in situ		A6H6 A9H9

Éénmalige melding met terugbetaling van HPV-testen en cytologische onderzoeken zolang er sprake is van een hoogrisico rekening houdend met de wetenschappelijke richtlijnen.

TIJDELIJK HOOGRISICO

Pseudocode	Indicatie	indicatie aanvinken	Nomenclatuurcode waarvan het gebruik wordt gemeld
A7H7	Tijdelijk hoogrisico (diagnostische of therapeutische opvolging)		A5H5 A8H8

Éénmalige melding met terugbetaling vanopvolgtesten (HPV en cytologie) tweemaal per kalenderjaar zolang er sprake is van een medisch noodzakelijke striktere opvolging dan éénmaal per kalenderjaar.

BEGINDATUM : .....

Identificatie van de verstrekker :

Naam: ..... Voornaam: .....

RIZIV-nummer: .....

Datum en handtekening: ..... STEMPEL: .....

[1] HIV positieve personen, na orgaantransplantatie, na allogenetische stamceltransplantatie, systemische lupus erythematosus, congenitale primaire immuundeficiëntie, patienten onder immuunsuppressieve behandeling voor inflammatoire darmaandoeningen, reumatologische aandoeningen, sarcoidosis of neuromyelitis optica

Post-colposcopy follow-up

- HPV+ (NILM/ASCUS/LSIL) with colposcopy CIN 0/1
  - HPV test at 12 months with reflex cytology
  - HPV16/18+ → repeat colposcopy
  - Non-HPV16/18+ → cytology
    - ASC-H/HSIL → repeat colposcopy
    - NILM/ASCUS/LSIL → repeat colposcopy

  - HPV negative → repeat HPV after 12 months (2x negative → routine screening)

- HPV+ ASC-H/HSIL with colposcopy CIN 0/1
  - Revise cytology
  - Exclude VaIN/uVIN/vHSIL/PaIN/AIN
  - If all negative: repeat colposcopy and HPV with reflex cytology in 6 months

- Colposcopy CIN2 <30y
  - Colposcopy every 5 months until no CIN2

- Colposcopy CIN2/3
  - Conisation
  - Follow-up HPV at 6 and 18 months

Other considerations

- Central registration
  - Information **to** BCR
    - Clinical biology labs: 'real time' through a FHIR protocol (not ready)
    - Pathology labs: usual data transfer 1x/month (now: 1x/3 months)
  - Information **from** BCR ('who is entitled to reimbursement?')
    - Not ready

- Co-payment/supplements
  - Not allowed in screening tests!

- Cost of consumables
  - 1,5€ to be charged to the molecular lab (unless they provide the material)

- BELAC (quality control)
  - Guideline should be ready 11/2024
  - TAT is important! (14 days HPV + 14 days cytology →integrated advice)

- Validated HPV tests (Sciensano website)

Assay	Manufacturer
Alinity m HR HPV Assay	Abbott, Wiesbaden, Germany
Allplex II HR	Seegene, Seoul, South Korea
Anyplex II HPV HR Detection	Seegene, Seoul, South Korea
APTIMA HPV Assay*	Hologic, Bedford, MA, USA
*in combination with another mRNA assay (APTIMA HPV16, 18, 45; Hologic) which can identify HPV16 and HPV18,45	
CLART HPV4S	GENOMICA SAU, Madrid, Spain
Cobas 4800 HPV Test	Roche Molecular System, Pleasanton, CF, USA
Cobas® HPV test (for use on the Cobas® 5800/6800/8800 Systems)	Roche Molecular System, Pleasanton, CF, USA
HPV-Risk Assay	Self-Screen BV, Amsterdam, The Netherlands
HPV Test Onclarity HPV Assay	BD Diagnostics, Sparks, MD, USA
NeuMoDX	Qiagen, Ann Arbor, MI, USA
RealTime High Risk HPV Test	Abbott, Wiesbaden, Germany
RIATOL HPV genotyping qPCR assay	in house, AML, Antwerp, Belgium
Xpert HPV	Cepheid, Sunnyvale, CA, USA

List of internationally validated hrHPV assays which can be applied in the Belgian cervical cancer screening (ordered alphabetically).
Updated on 05/08/2024.

Primary HPV screening: conclusions

- Complicated nomenclature and clinical guideline!
  - Lots of conflict between RIZIV/INAMI and Sciensano guideline
  - Physicians could be tempted to order a lot of co-testing (for the sake of simplicity)
- Nomenclature changes from 1-1-2025
  - E.g. no longer use the ‘second reading’ of cytology
- Introduction of co-testing in the nomenclature

Primary HPV screening: conclusions

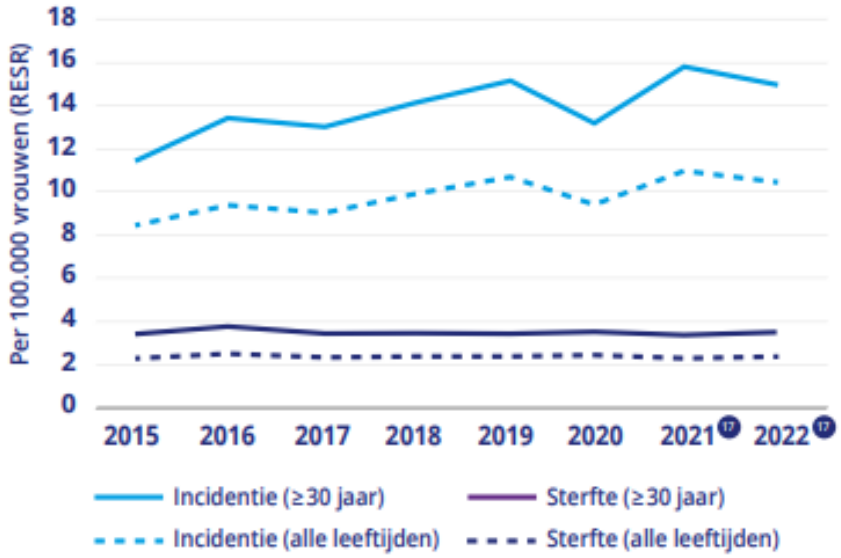
- Self sampling
  - Regional responsability
  - Flanders: test project results expected end 2025
  - If self sample positive → clinical sample by a physician
  - Netherlands: about 55% self samples in 2023 (personal communication)

- Reimbursement: prepare yourself!
  - No central registration for now
  - Notification form (to be send by physician to insurance company)
  - Request form
  - Good communication between labs (TAT 14+14 days!)

What to expect in the next 3-5 years?

- Drop in cytology tests
  - Netherlands: about 35% of tests remain (personal communication)
- Drop in screening attendance
  - Netherlands: >70% (2016) → 46% (2022)
  - Flanders: about 60% (2022)
  - Br/Wa: <50% (2022)
- Sharp rise in colposcopy + biopsies
  - Netherlands: +300%
- Rise of cervical cancer cases?
  - Netherlands: rising trend

Figuur 12 / **Incidentie en sterfte baarmoederhalskanker in Nederland** naar jaar (bron: NKR (incidentiecijfers) en CBS (sterftecijfers))




THE OTHER WAY
THIS WAY
THAT WAY