CANCER CENTRE

INTRODUCTION OF THE HPV TEST IN CERVICAL CANCER SCREENING IN BELGIUM

In December 2022, the Interministerial Conference (IMC) of Public Health decided (in line with the IMC's earlier decisions during the previous reign) to switch from cytology to primary HPV screening for cervical cancer (from the age of 30 onwards). This decision is based on available scientific evidence ranging from the 2015 KCE report 238 to very recent analyses conducted by the World Health Organisation (WHO) and the International Agency for Research on Cancer (IARC). This shift will become effective on 01/01/2025.

We herewith provide you with a brief overview of the clinical guidelines accompanying the new screening algorithms, the nomenclature changes, the list of accepted HPV tests, special provisions for accreditation of medical laboratories and regulations on the registration of the screening results. From December 2024 onwards, all information will be summarised on Cervical cancer screening | sciensano.be.

A. Clinical guidelines

TABLE 1: NEW TEST SCHEME: PRIMARY SCREENING & REFLEX TESTING (TRIAGE)

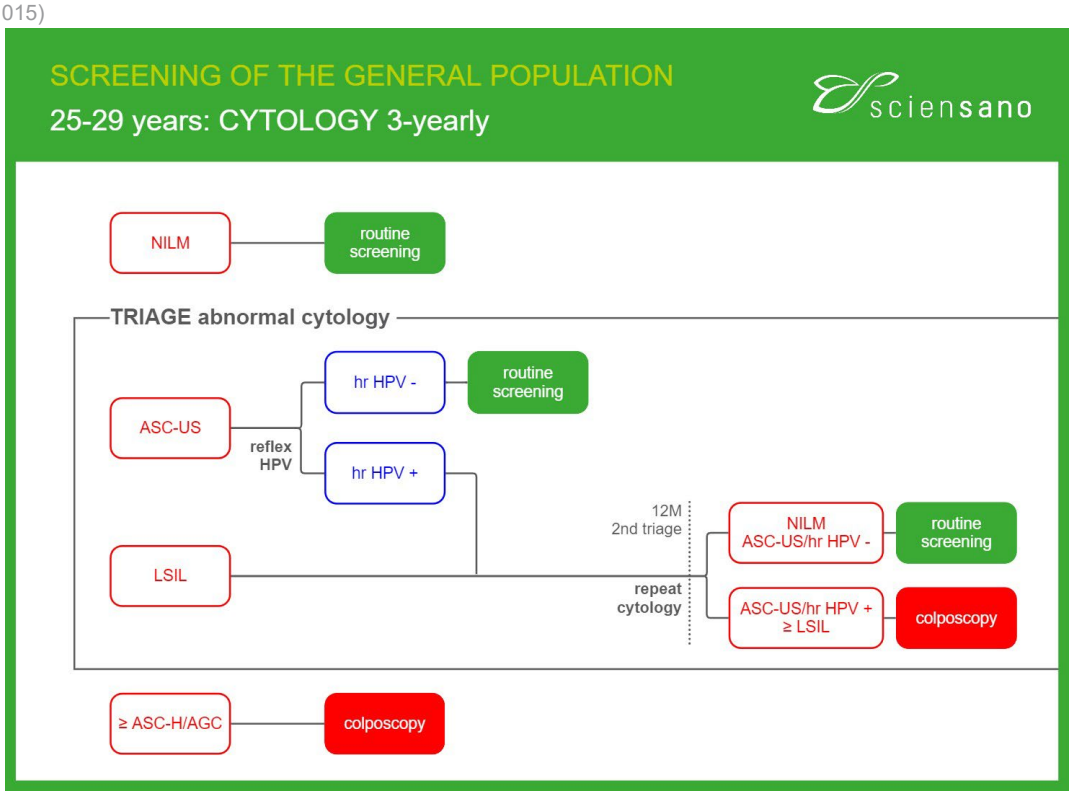
Age category	Primary screening	Frequency	Triage - reflex test (after a positive primary test)	2nd triage - repeat testing (in 12 months)
≤24y	No	NA	NA	NA
25-29y *(Figure 1)*	Cytology	Every 3 calendar years	ASC-US result -> HPV test	hrHPV pos. -> repeat cytology Primary screening result LSIL -> repeat cytology
30-64y *(Figure 2)*	HPV test	Every 5 calendar years	hrHPV non-16/18 pos. -> cytology (not as triage : HPV16/18 pos. -> cytology + colposcopy)	NILM result -> HPV test
65+ (exit or catch-up screening)[1]	Cotesting (cytology+HPV), on the same sample	Once	NA	hrHPV non-16/18 pos. + NILM -> HPV test hrHPV neg. + ASC-US -> HPV test

[1] If no screening was reimbursed in the previous 10 years.

The technique of sample taking does not change. To avoid having to take another sample from the woman after a positive primary screening test, the physician will use a specific cervical swab/brush with an accompanying bottle of liquid in which the endocervical cells are stored so that both examinations (initial screening and reflex triage) are performed on the same sample.

Unless otherwise specified by the laboratory, physicians can keep on sending the samples to their usual laboratory (Pathological Anatomy or Clinical Biology). Labs are responsible for transferring the sample to another lab if they are not able/accredited to perform the necessary test(s).

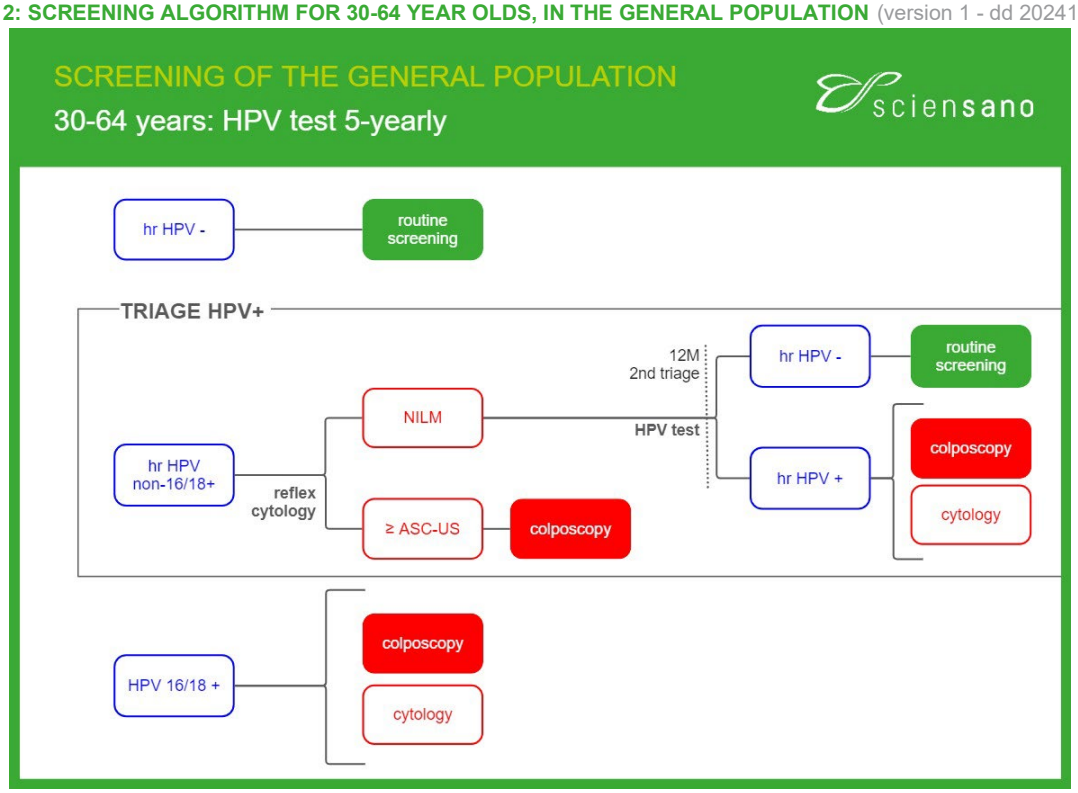
FIGURE 1: SCREENING ALGORITHM FOR 25-29 YEAR OLDS, IN THE GENERAL POPULATION (version 1 - dd 20241015)



≥ASC-H/AGC = ASC-H/AGC or a more severe abnormality (HSIL, SCC, AIS, AC)

Remark: An ASC-US result is always followed by a reflex HPV test (both in primary screening and in 2nd triage 12 months later)

FIGURE 2: SCREENING ALGORITHM FOR 30-64 YEAR OLDS, IN THE GENERAL POPULATION (version 1 - dd 20241015)



Remark: A hrHPV positive result is always followed by a reflex cytology (both in primary screening and 2nd triage 12 months later)

An integrated advice shall be formulated by the laboratory that performed the primary screening test.

The reflex test result is transferred to the healthcare provider who performed the primary screening test. Based on both results, the primary laboratory will provide a recommendation regarding the further therapeutic approach to follow (= integrated advice) to the requesting physician and - in the future - to the Belgian Cancer Registry (BCR).

TABLE 2: INTEGRATED ADVICE – 25-29 AND 30-64 YEAR OLDS (ANNEX 1)

TABLE 3: NEW TEST SCHEME : FOLLOW-UP, CLINICAL TESTING (WITH SYMPTOMS) AND HIGH-RISK GROUPS

FOLLOW-UP			
	Test type	**Frequency reimbursement**	**Notification advising phycisian**
Diagnostic or therapeutic follow-up	Cytology and/or HPV-test (not to be interpreted as cotesting)	One reimbursement/calendar year, both for cytology and HPV-testing	Temporary high-risk with the possibility of testing twice per calendar year (e.g. in HSIL without treatment)
CLINICAL/DIAGNOSTIC			
Clinical testing (with symptoms)[2]	Cotesting (cytology + HPV)	No limitation	Notification with reimbursement of one diagnostic cotest
HIGH-RISK GROUPS			
DES[3] AIS[4]	Cotesting (cytology + HPV)	No limitation Recommendation: yearly	Notification with reimbursement of all required tests
Others[5] (immunocompromised)	HPV-test or cytology, depending on age	No limitation Recommendation: 3-yearly HPV-test or yearly cytology, depending on age[◊]	Notification with reimbursement of all required tests

[2] indications: postmenopausal blood loss, abnormal therapy-resistant uterine blood loss, unexplained postcoital blood loss

[3] DES=diethylstilbestrol: synthetic estrogen prescribed to pregnant women between 1938 and 1971 to prevent miscarriage. The daughters of DES-treated women are at higher risk of cancers including cervical cancer.

[4] AIS=adenocarcinoma in situ

[5] UPDATED DEFINITION vs nomenclature: all patients with immunosuppression (HIV positives (CD4 <350/µl or HIVRNA >200 cp/ml), after organ transplantation, after allogenetic stem cell transplantation, systemic lupus erythematosus, congenital primary immune deficiency, or patients under long-term continued immunosuppressants) require more frequent screening, as long as the immunosuppressive treatment is continued.

[◊] *Cfr Clinical Guidance; 3.4 Screening, triage and follow-up in high-risk populations (to be published at* Cervical cancer screening | sciensano.be*)*

To obtain reimbursement for clinical/diagnostic testing as well as for high-risk groups and in case of temporary high-risk, the prescribing physician will complete a standardised notification form and ticks the corresponding indication (RIZIV/INAMI will detail the notification form in a future publication).

B. Nomenclature changes

The **nomenclature of Article 3** for the collection of a cervicovaginal smear will be adapted. To the existing nomenclature (screening and diagnostic/therapeutic follow-up) a third provision will be added for clinical/diagnostic examination (suspicious symptomatology) including screening of high-risk groups. For the existing screening nomenclature codes, application rules clarify the frequency of charging by age group.

	NOMENCLATURE CODES: SMEAR COLLECTION	General practitioner	Gynaecologist
1	Screening	114030-114041	149612-149623
2	Follow-up: diagnostic/therapeutic	114170-114181	149634-149645
3	**NEW: clinical/diagnostic + high-risk groups**	**114192-114203**	**149656-149660**

The **nomenclature of Article 14, g)** will also be adjusted (431955-431966), in particular the fee for colposcopy will significantly increase. At the same time, quality requirements will be imposed with:

1) mandatory participation in a validated colposcopy course or obtaining a colposcopy certificate for the performing gynaecologist, organised by VVOG/CRGOLFB;
2) mandatory storage of interpretable images in the patient's medical record;
3) a mandatory standardised report containing the EFC minimal requirements for describing the colposcopic examination (a report template will be provided within the Clinical Guidance, to be published at Cervical cancer screening | sciensano.be).

The nomenclature in the context of HPV testing will be transferred **from article 32 to article 24bis**. This nomenclature of article 24bis is accessible to both pathologists and clinical biologists.

Article 24bis nomenclature provides four separate codes for the **HPV test**:

	NOMENCLATURE CODES: HPV-test	
1	Primary HPV screening in 30- to 64-year-olds and once in insured women aged 65 and over$^{\Delta}$	553615-553626
2	Reflex HPV test in case of abnormal cytology in 25- to 29-year-olds	553630-553641
3	Diagnostic or therapeutic follow-up: once a year (unless notification and temporary high-risk)	553652-553663
4	With clinical symptoms and testing of high-risk groups (via notification)	553674-553685

The adapted nomenclature of Article 32 (only accessible for pathologists) provides four separate codes for **cytology**:

	NOMENCLATURE CODES: CYTOLOGY	
1	Primary screening by cytology in 25- to 29-year-olds and once in insured women aged 65 and over$^{\Delta}$	589853-589864
2	Reflex cytology after a positive HPV test in 30- to 64-year-olds	591791-591802
3	Diagnostic or therapeutic follow-up: once a year (unless notification and temporary high-risk)	591813-591824
4	With clinical symptoms and testing of high-risk groups (via notification)	591835-591846

$^{\Delta}$ If no screening was reimbursed in the previous 10 years.

Co-payments and supplements

The Royal Decree of 30 October 2017 (BS 30/10/2017, numac 2017013750) stipulates that **no supplements** will be charged for medical services provided **in the context of organised screening programmes.**

As part of primary screening, the aim is to limit the co-payment to keep the threshold for participation as low as possible (co-payment only for the doctor's consultation).

Transitional arrangement

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. 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. This means

that women with a previous negative reflex HPV test result or a not-reimbursed negative HPV test result (and normal cytology) should only be advised for the next screening round in 5 years time.

C. List of accepted HPV tests

The list of internationally validated high-risk HPV tests that can be used in cervical cancer screening in Belgium can be found at National Reference Center (NRC) for Human papillomavirus | sciensano.be

This table contains a dynamic list of molecular tests for the detection of high-risk HPV and will be updated at least twice a year as new scientific evidence becomes available.

D. Special provisions for accreditation of medical laboratories (BELAC)

To ensure the quality of the HPV tests and analyses, the HPV tests must be performed in a laboratory recognised as a clinical biology or pathological anatomy laboratory by the Minister of Public Health. The laboratory must also hold ISO 15189 accreditation for the molecular tests performed from art24bis. The laboratory must moreover submit to the quality controls carried out by Sciensano. Moreover, labs should be specifically accredited for a validated test from the NRC-HPV list above.

As for cytology, BELAC accreditation according to ISO 15189 cannot be imposed by law. The quality of gynaecological cytology is again monitored by Sciensano.

BELAC will publish a guideline within the body of 2-405 documents (by December 2024), making these provisions binding on laboratories seeking ISO 15189 accreditation for the respective services within cervical cancer screening and triage that fall within the scope of the ISO 15189 standard.

E. Registration of screening results

The results of screening are required to be registered, in accordance with Article 5a) of Article 24bis of the nomenclature.

In future, a system-to-system registration from the laboratories to the Belgian Cancer Registry (BCR) will be pursued. This is required for all results for cervical samples, not restricted to those in the context of screening.

Laboratories for Pathological Anatomy to BCR

Laboratories deliver 2 separate files: a structured file with all variables and a file with the written reports (protocols) monthly to BCR. In future, maximum efforts will be made for continuous delivery of individual results; processing via new FHIR architecture. BCR will implement a minimal extension to the current Cervibase coding, to allow reporting on ‘HPV-only (i.e. cytology not performed)’ in the CODAP/SNOMED lesion codes.

Laboratories for Clinical Biology to BCR

BCR receives a copy of all validated results when they are sent to the requesting physician (= continuous delivery). For this purpose, individual results are sent as structured messages, conforming to the HL7-FHIR standard.

Annex 1

TABLE 2: INTEGRATED ADVICE – 25-29 AND 30-64 YEAR OLDS

Age range: 25-29 years					
Result cytological examination	**Result reflex hrHPV test**	**(Integrated) advice**	**Result 2nd triage (in 12 months)**	**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**	--> 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	**Immediate referral for colposcopic examination**
			--> ≥ LSIL		Immediate referral for colposcopic examination
LSIL	NA	Repeat cytology in 12 months	--> 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	**Immediate referral for colposcopic examination**
			--> ≥ LSIL		Immediate referral for colposcopic examination
≥ ASC-H/AGC	NA	Immediate referral for colposcopic examination		NA	
INSU	NA	New sampling after 6 weeks at the earliest		NA	

Age range: 30-64 years					
Result hrHPV test	**Result reflex cytology**	**(Integrated) advice**	**Result 2nd triage (in 12 months)**	**(Result reflex cytology)**	**Advice**
hrHPV negative	NA	Regular screening interval (in 5 calendar years)			
hrHPV non-16/18 positive		**Result of reflex cytology, with recommendation, will follow**			
	--> ≥ ASC-US	**Immediate referral for colposcopic examination**			
	--> NILM	**Repeat hrHPV testing in 12 months**	--> hrHPV negative		Regular screening interval (in 5 calendar years)
			--> hrHPV positive	(cytology, not as triage)	Immediate referral for colposcopic examination
					Result of reflex cytology will follow
HPV 16/18 positive	(cytology, not as triage)	Immediate referral for colposcopic examination			
		Result of reflex cytology will follow			
HPVi		New sampling after 6 weeks at the earliest			

≥ASC-H/AGC = ASC-H/AGC or a more severe abnormality (HSIL, SCC, AIS, AC)

NB: Immediate referral for colposcopic examination is understood within 3 months or faster, according to the severity of the screen-positive result *(Cfr Clinical Guidance; 5.3. Good clinical practice (to be published at* Cervical cancer screening | sciensano.be*)*.
Cave: If on cytological examination normal endometrial cells are found in an entitled person > 45 years, additional advice is given: 'Correlation with clinic is indicated to exclude endometrial pathology'.
Cave: If on cytological examination abnormal endometrial cells are found in an entitled person > 45 years, additional advice is given: 'Exploration to exclude endometrial pathology'

CONTACT

For general questions:
Cindy Simoens * cindy.simoens@sciensano.be

For specific profession-related issues:
info@belgian-society-pathology.eu
vbsgbs.pathologie@telenet.be

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