CALL FOR STAKEHOLDER COMMENTS ON THE PRELIMINARY RECOMMENDATION OF THE HEALTH TECHNOLOGY ASSESSMENT (HTA) COUNCIL ON *HIGH RISK HUMAN PAPILLOMAVIRUS VIRUS (HrHPV) DNA TEST and VISUAL INSPECTION WITH ACETIC ACID (VIA)*

Published as of 11 February 2025

As of 11 February 2025, the Health Technology Assessment (HTA) Council hereby makes public its preliminary recommendations on the possible financing of **High Risk Human Papillomavirus (HrHPV) DNA Test** and **Visual Inspection with Acetic Acid (VIA)** by Department of Health (DOH) and/or PhilHealth, for stakeholder feedback/comments.

These health technologies were reviewed in the light of the Philippine Food and Drug Administration (FDA) requirements for authorization, existing recommendations by the World Health Organization (WHO), inclusion in the WHO Essential Diagnostics List (EDL), clinical practice guidelines (CPGs) *[local and approved by the DOH; and international guidelines],* and DOH Omnibus Health Guidelines (OHG), and existing economic evaluation (EE) studies. Aside from reviewing existing economic evaluation (EE) studies, costing analyses of these health technologies were performed. The supporting evidence reviewed and discussed by the HTA Council are shown in **Annex A.**

1. High Risk Human Papillomavirus Virus (HrHPV) DNA Test

The HrHPV DNA test is positively recommended for cervical cancer screening in women ages 30-65 years, every 5 years as long as the test adheres to the **minimal** characteristics specified in the WHO Target product profiles (TPPs) for human papillomavirus screening tests to detect cervical pre-cancer and cancer (2024) *(Refer to Annex A1 for TPP of HPV screening test for use in laboratories and Annex A2 for TPP of HPV screening test for use at point of care),* noting the VALGENT (2016) protocol cited by WHO for the clinical validation of HPV assays *(i.e., in interpreting values for relative clinical sensitivity and specificity, lower bound confidence intervals should be compared against the TPP).* Second-generation comparator tests fulfilling new international criteria as indicated in Arbyn, et. al., (2024) should be used for validation of novel HPV DNA tests.

HrHPV DNA Testing is recommended in the WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, 2nd edition (2021). It is also included in the Philippine DOH Omnibus Health Guidelines for Adults (2023) citing the PHEX: HPV Testing, Cytology, Co-Testing, or VIA in Screening for Cervical Cancer (2021) as their evidentiary basis. The Philippine Obstetrical and Gynecological Society (POGS) also adopted the WHO recommendation and released an E-Primer on the use of HPV Testing (2022).

Based on systematic search of EE studies from lower-middle income countries (LMICs), three (3) studies reported that HPV DNA tests with varying frequencies were cost-effective (Lobin et al., 2024; Casas et al., 2022; Sharma et al., 2017). Further, Casas et al., 2022 reported that primary HPV DNA test is the most cost-effective strategy in India, Uganda, and Nicaragua. One study [Goldie et al (2005)] found both one-time VIA and one-time HPV DNA tests as cost-effective strategies in Peru and Thailand. According to the WHO Syntheses of Evidence for the guidelines for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention second edition (2021), primary HPV DNA test without triage was the most cost-effective approach in general. However, primary HPV DNA test with 16/18 triage was very close in terms of costs and effects and had a better balance of benefits to harms. Lastly, the economic evaluation of an HTA by Malaysia MaHTAs (2011) also recommends HPV DNA-based testing to be conducted with varying frequencies.

Based on comparative costing:

- **Cost of HPV Screening per Person:**
  - Intervention 1A: HPV DNA test screening with non-specific genotyping - **[Redacted]**
  - Intervention 1B: HPV DNA test with specific genotyping (HPV 16/18) - **[Redacted]**

- **Annual Cost of HPV Screening for the intended population** *(sample scenarios of screening transition from small scale implementation of HrHPV DNA Test combined with VIA to full implementation of HrHPV DNA Testing)***:**
  - **Algorithm 1** (Intervention 1A [HPV DNA Test screening with non-specific genotyping] + Intervention 2 [VIA screening] → Intervention 1A):
    - **Scenario 1** (50% Intervention 1A + 50% Intervention 2): **Php 19,176,251,600.00**
    - **Scenario 2** (75% Intervention 1A + 25% Intervention 2): **Php 27,658,265,800.00**
    - **Scenario 3** (100% Intervention 1A): **Php 36,140,280,000.00**
  - **Algorithm 2** (Intervention 1B [HPV DNA Test with specific genotyping (HPV 16/18)] + Intervention 2 [VIA (screening] → Intervention 1B):
    - **Scenario 1** (50% Intervention 1B + 50% Intervention 2): **Php 9,939,781,676.00**
    - **Scenario 2** (75% Intervention 1B + 25% Intervention 2): **Php 13,803,560,914.00**
    - **Scenario 3** (100% Intervention 1B): **17,667,340,152.00**

The above costs account for the costs of the screening tests only. The scenarios above are simulated for the purpose of the HTA Council's evaluation, and do not reflect the actual implementation plans of the program. The specific screening approach shall be up to the national government, depending on capacity and budget availability.

2. **Visual Inspection with Acetic Acid (VIA)**

VIA is positively recommended for cervical cancer screening in women ages 30-65 years every 3 years, in settings wherein HPV DNA testing is still not operational.

VIA is recommended in the WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, 2nd edition (2021). It is also included in the Philippine DOH Omnibus Health Guidelines for Adults (2023) citing the PHEX: HPV Testing, Cytology, Co-Testing, or VIA in Screening for Cervical Cancer (2021). It is also recommended by the Society of Gynecologic Oncologists of the Philippines Inc (SGOP) (2019) based on the Clinical Practice Guidelines for Obstetrician – Gynecologists (2019).

Based on a systematic search of EE studies, three (3) out of five (5) cost-effectiveness analysis (CEA) studies reported that VIA with varying frequencies (i.e., 3 years in Western Kenya, 5 years in India, one-time visit in India, Kenya and Peru) was the most cost-effective strategy (Lobin et al., 2024; Chauhan et al., 2020; Goldie et al., 2005). The study of Goldie et al (2005) found both one-time VIA and one-time HPV DNA tests as cost-effective strategies in Peru and Thailand.

The **cost of screening with VIA per person** is **[Redacted]**. However, in the Philippines, following the global recommendations, the DOH does not plan to implement VIA alone but will only serve as either (1) triage to HrHPV DNA testing or an (2) alternative to HrHPV DNA Testing in some areas.

As such, below are the estimated annual screening cost of implementing VIA together with HPV DNA testing:

- **Annual Cost of HPV Screening for the intended population** *(sample scenarios of screening implementation plans which present the complementary role of VIA to the implementation of HrHPV DNA Test*:
  - **Algorithm 1** (Intervention 1A [HPV DNA Test screening with non specific genotyping] + Intervention 2 [VIA screening] → Intervention 1A):
    - **Scenario 1** (50% Intervention 1A + 50% Intervention 2): **Php 19,176,251,600.00**
    - **Scenario 2** (75% Intervention 1A + 25% Intervention 2): **Php 27,658,265,800.00**
  - **Algorithm 2** (Intervention 1B [HPV DNA Test with specific genotyping (16/18)] + Intervention 2 [VIA (screening] → Intervention 1B):
    - **Scenario 1** (50% Intervention 1B + 50% Intervention 2): **Php 9,939,781,676.00**
    - **Scenario 2** (75% Intervention 1B + 25% Intervention 2): **Php 13,803,560,914.00**

Similar to the costing performed for HrHPV DNA Test the above costs account for the costs of the screening tests only and the scenarios do not reflect the actual implementation plans of the program. The specific screening approach shall be up to the national government, depending on the capacity and budget availability.

For the supporting evidence reviewed and discussed by the HTA Council, please refer to: https://bit.ly/PrelimRecomHrHPVDNATestxVIA.

All comments, inputs, and/or appeals on the above preliminary recommendation may be submitted until **25 February 2025 (Tuesday)**, for the consideration of the HTA Council, through email at hta@dost.gov.ph.

Please use the prescribed form for appeals indicated in the official HTA Philippines website [https://hta.dost.gov.ph/appeals-2/]. **Appeals not following the prescribed format, and those submitted beyond the deadline shall not be entertained**.

Should you have any questions or concerns regarding the preliminary recommendation, please contact us through the same email address or via telephone call via (02) 8837 2071 local 4100.

Thank you very much.

On behalf of the HTA Philippines:

ANNE JULIENNE G. MARFORI, RPh, MSc
Division Chief, HTA Division

JACINTO BLAS V. MANTARING III, MD, MSc
Chairperson, HTA Council

Annex A. Summary of Evidence for the Preliminary Recommendation of Priority Topics

	High Risk Human Papillomavirus Virus (HrHPV) DNA Test for cervical cancer screening in women ages 30-65 years	**Visual Inspection with Acetic Acid (VIA)** for cervical cancer screening in women ages 30-65 years in settings wherein HPV DNA testing is still not operational
Philippine FDA certification	Not yet registrable based on the FDA Memorandum Circular 2014 - 005 with subject *"Updated List of Medical Devices required to be be registered prior to sale, distribution, and use"*	*Not applicable*
WHO Essential Device List	Included in the WHO Technical Report Series 1053: The selection and use of essential in vitro diagnostics: *"Table II.b. Disease-specific IVDs recommended for use in clinical laboratories* ***Human papillomavirus (HPV) infection*** - *IVD Test: HPV nucleic acid test (NAT)* - *Test purpose: For cervical cancer screening*	
Clinical Practice Guidelines	Included in the Philippine DOH Omnibus Health Guidelines for Adults (2023) citing the PHEX: HPV Testing, Cytology, Co-Testing, or VIA in Screening for Cervical Cancer (2021) *(strong recommendation)* *"Table 5. Screening Laboratory Tests and Procedures* ***Cervical Cancer*** - *Eligible population: Women aged 30 to 65 years old* - *Screening Test to be Offered at Primary Care: Every 3 years with cervical cytology alone or every 5 years with high-risk HPV testing alone* *OR* *Every 5 years with high-risk HPV testing in combination with cytology (co-testing)* *OR* *Every 3 years using visual inspection with acetic acid, as an alternative to Pap smear, among asymptomatic women* The Philippine Obstetrical and Gynecological Society (POGS) also adopts the WHO recommendation and released an E-Primer on the use of HPV Testing (2022) *[page 8]*:	Included in the Philippine DOH Omnibus Health Guidelines for Adults (2023) citing the PHEX: HPV Testing, Cytology, Co-Testing, or VIA in Screening for Cervical Cancer (2021) *(strong recommendation)* *"Table 5. Screening Laboratory Tests and Procedures* ***Cervical Cancer*** - *Eligible population: Women aged 30 to 65 years old* - *Screening Test to be Offered at Primary Care: Every 3 years with cervical cytology alone or every 5 years with high-risk HPV testing alone* *OR* *Every 5 years with high-risk HPV testing in combination with cytology (co-testing)* *OR* *Every 3 years using visual inspection with acetic acid, as an alternative to Pap smear, among asymptomatic women"* Recommended by the Society of Gynecologic Oncologists of the Philippines Inc (SGOP) (2019) based on the Clinical Practice Guidelines for Obstetrician – Gynecologists (2019):

	"The WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV. Existing programs using cytology and visual inspection with acetic acid (VIA) should transition when HPV DNA testing becomes available. This is considered a shift in care." *"The screening interval suggested is every 5 years when using HPV DNA testing as primary screening tool. This is based on modelling studies showing that such interval may result in greater benefits, fewer harms and lower costs than a 10-year interval."*	*"In low resource settings, visual inspection with acetic acid (VIA) may be done as an acceptable alternative to pap smear."*
WHO recommendation	Recommended by the WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, 2nd edition (2021) *(Strong recommendation, moderate certainty evidence) [page 11]:* *"WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV."* The WHO has released the WHO Target product profiles (TPP) for human papillomavirus screening tests to detect cervical pre-cancer and cancer (2024) which recommends the minimal and preferred characteristics of HPV tests *(See Annex A1 for **Table 4.1 TPP for HPV screening tests for use in laboratories** and Annex A2 for **Table 2.2. TPP for HPV screening tests for use at the point of care**) [page 17-32]*	Recommended in the WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, 2nd edition (2021) *(Conditional recommendation, low-certainty evidence)*: *"Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every 3 years when using VIA or cytology as the primary screening test, among both the general population of women and women living with HIV."*
Review of available EE studies	Three out of five studies (Lobin et al., 2024; Casas et al., 2022; Sharma et al., 2017) reported that HPV DNA test (with varying frequencies) was cost-effective. Casas et al., 2022 specifically pointed out primary HPV DNA test as the most cost-effective strategy in India, Uganda, and Nicaragua. Goldie et al (2005) found both one-time VIA and one-time HPV DNA tests as cost-effective strategies in Peru and Thailand. According to the WHO Syntheses of Evidence for the guidelines for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention,second edition (2021), primary HPV DNA test screening approaches	Three (3) out of five (5) CEA studies reported that VIA with varying frequencies (i.e., 3 years in Western Kenya, 5 years in India, one-time visit in India, Kenya and Peru) was the most cost-effective strategy (Lobin et al., 2024; Chauhan, et al., 2020; Goldie et al., 2005). The study of Goldie et al (2005) found both one-time VIA and one-time HPV DNA tests as cost-effective strategies in Peru and Thailand.

	were the most effective compared to other primary screening approaches. Primary HPV DNA test without triage was the most cost-effective approach in general. However, primary HPV DNA test with 16/18 triage was very close in terms of costs and effects and had a better balance of benefits to harms. An HTA assessment by Malaysia MaHTAs in 2011 recommends HPV DNA-based testing to be conducted with varying frequencies: *"a) every five years as a primary screening strategy,* *b) every three to five years when combined with Pap test in women over 30 years of age in women who are negative on both tests in the annual screening, or* *c) a single lifetime screening."*	

Costing	Based on comparative costing:
	
	• **Cost of Screening per Person:**
	  ○ Intervention 1A: HPV DNA test screening with non specific genotyping - **[Redacted]**
	  ○ Intervention 1B: HPV DNA test with specific genotyping (16/18) - **[Redacted]**
	
	• **Annual Cost of HPV Screening for the intended population** *(sample scenarios of screening transition from small scale implementation of HrHPV DNA Test combined with VIA to full implementation of HrHPV DNA Testing)*:
	  ○ **Algorithm 1** (Intervention 1A [HPV DNA Test screening with non specific genotyping] + Intervention 2 [VIA screening] → Intervention 1A):
	  ▪ **Scenario 1** (50% Intervention 1A + 50% Intervention 2): **Php 19,176,251,600.00**
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	  ▪ **Scenario 3** (100% Intervention 1A): **Php 36,140,280,000.00**
	  ○ **Algorithm 2** (Intervention 1B [HPV DNA Test with specific genotyping (16/18)] + Intervention 2 [VIA (screening] → Intervention 1B):
	  ▪ **Scenario 1** (50% Intervention 1B + 50% Intervention 2): **Php 9,939,781,676.00**
		The **cost of screening with VIA per person** is **[Redacted].** However, in the Philippines, following the global recommendations, the DOH does not plan to implement VIA alone but will only serve as either (1) triage to HrHPV DNA testing or an (2) alternative to HrHPV DNA Testing in some areas. As such, below are the estimated annual screening cost of implementing VIA together with HPV DNA testing:
		
		• **Annual Cost of HPV Screening for the intended population** *(sample scenarios of screening implementation plans which present the complementary role of VIA to the implementation of HrHPV DNA Test:*
		  ○ **Algorithm 1** (Intervention 1A [HPV DNA Test screening with non specific genotyping] + Intervention 2 [VIA screening] → Intervention 1A):
		  ▪ **Scenario 1** (50% Intervention 1A + 50% Intervention 2): **Php 19,176,251,600.00**
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		  ○ **Algorithm 2** (Intervention 1B [HPV DNA Test with specific genotyping (16/18)] + Intervention 2 [VIA (screening] → Intervention 1B):
		  ▪ **Scenario 1** (50% Intervention 1B + 50% Intervention 2): **Php 9,939,781,676.00**
		  ▪ **Scenario 2** (75% Intervention 1B + 25% Intervention 2): **Php 13,803,560,914.00**
		
		Similar to the costing performed for HrHPV DNA Test the above costs account for the costs of the screening tests only and the scenarios do not reflect the actual implementation plans of the program. The specific screening

	■ **Scenario 2** (75% Intervention 1B + 25% Intervention 2): **Php 13,803,560,914.00** ■ **Scenario 3** (100% Intervention 1B): **17,667,340,152.00** The above costs account for the costs of the screening tests only. The scenarios above are simulated for the purpose of the HTA Council's evaluation, and do not reflect the actual implementation plans of the program. The specific screening approach shall be up to the national government, depending on the capacity and budget availability.	approach shall be up to the national government, depending on the capacity and budget availability.

Annex A1. TPP for HPV screening tests for use in laboratories

Characteristic	Minimal	Preferred
Scope		
Intended use	HPV screening for cervical pre-cancer and cancer detection	Same as minimal
Target population	Women and individuals with a cervix age 30 or older, and age 25 or older for those living with HIV	Same as minimal
Target use setting	Level 2–4 health-care settings and laboratories	Same as minimal
Specimen taker/ specimen type [a]	A test that is validated for ONE of the following: ▪ a **vaginal** sample self-collected by the participant ▪ a **vaginal** sample collected by a health worker (without speculum) ▪ a **cervical** sample collected by a health worker	A test that is validated for ALL of the following: ▪ a **vaginal** sample self-collected by the participant ▪ a **vaginal** sample collected by a health worker (without speculum) ▪ a **cervical** sample collected by a health worker
	Annotation: *The collection of a vaginal sample (either by a health worker or by self-collection) does not require visualization of the cervix. The vaginal sample can be collected in the health facility or at home. The collection of a cervical sample requires exposing the cervix with a speculum, inserted by a health worker.*	
Specimen tester	A test that can be performed by a lab-trained health worker.	Same as minimal

Characteristic	Minimal	Preferred
Technical specifications		
Target analyte type	Qualitative detection of HPV DNA or mRNA [b]	Same as minimal
	Annotation: *Aligning with the guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, these TPPs focus on HPV NATs, targeting HPV DNA or mRNA, as do most available tests and those in the pipeline. However, we do not discourage research on tests focusing on different targets. Any forthcoming guideline update will be followed by an update to the TPP.*	
Genotype spectrum	▪ 8 cHPV types: carcinogenic groups (most carcinogenic first) – 1a [16]; 1b [18, 45]; 1c [33, 58, 31, 52, 35] ▪ Probably (Group 2A) and possibly (Group 2B) carcinogenic HPV types, including 68 and 66, should be excluded from screening tests	▪ 12 cHPV types: carcinogenic groups (most carcinogenic first) – 1a [16];1b [18, 45]; 1c [33, 58, 31, 52, 35]; 1d [59, 39, 51, 56] ▪ Probably (Group 2A) and possibly (Group 2B) carcinogenic HPV types, including 68 and 66, should be excluded from screening tests
	Annotation: *Carcinogenic HPV type groups 1a, 1b, 1c and 1d are adapted from the IARC colour-coded classification (https://publications.iarc.fr/604) (11) (see Table 1.2).*	
Result output/ target – individual genotyping	At least 2-signal output (excluding control and/or negative): 1. Carcinogenic group 1a [16] individually; or grouped with group 1b [18, 45] pooled or individual 2. Carcinogenic group 1c [33, 58, 31, 52, 35] pooled	At least 4-signal output (excluding control and/or negative): 1. Carcinogenic group 1a [16] 2. Carcinogenic group 1b [18, 45] pooled or individual 3. Carcinogenic group 1c [33, 58, 31, 52, 35] pooled 4. Carcinogenic group 1d [59, 39, 51, 56] pooled
	Annotation: *HPV45 can be pooled with either HPV18 or 1c HPV group signal output.*	
Test kit format	If the assay requires separate nucleic acid extraction, the assay should be compatible with a range of standard extraction methods (but extraction reagents do not need to be included). The manufacturer should provide all required reagents for amplification (if applicable) and detection – preferably in one kit (sample collection and sample transport preservative, if applicable, do not need to be included).	Assay in which reagents for sample preparation (including nucleic acid extraction) and amplification, if applicable, and detection are all included and used on an automated system.
Instrument	Open or closed molecular systems are acceptable.	Capacity to detect other agents/diseases.

Characteristic	Minimal	Preferred
Need for additional equipment	If the assay requires separate nucleic acid extraction, any additional equipment should be compatible with automated workflows in wide use, without the need for additional proprietary extraction instrumentation. For polymerase chain reaction (PCR)-based assays, manufacturers should ensure the assay is compatible with off-the-shelf equipment for amplification/detection (i.e. at least one of the most widely used thermocyclers).	None needed.
Performance		
Cross-reactivity	Assay should not cross-react with: ▪ other common non-HPV microorganisms that can infect the genital tract ▪ non-targeted phylogenetically-related HPV genotypes < 2%	Assay should not cross-react with: ▪ other common non-HPV microorganisms that can infect the genital tract ▪ non-targeted phylogenetically-related HPV genotypes < 1%
Interference	Assay performance should not be impacted by common interfering substances present in the female genital tract.	Same as minimal.
Relative clinical sensitivity	***Definition:*** *The ability of the HPV test under evaluation to test positive among women with underlying cervical disease, using histologically confirmed cervical intraepithelial neoplasia (CIN)2+ and/or CIN3+, associated with one of the cHPV types targeted by the test, compared to same ability of a comparator HPV test. Values do not represent point estimates, but the lower bound of their confidence interval (38). Second-generation comparator tests fulfilling new international criteria would be used for validation of novel HPV DNA tests (39).*	
	CIN2+: 0.90 [c] CIN3+: 0.95 [c]	CIN2+: 0.95 CIN3+: 0.98
Relative clinical specificity	***Definition:*** *The ability of the HPV test under evaluation to test negative among women without underlying clinically significant cervical disease, compared to same ability of a comparator HPV test. Values do not represent point estimates, but the lower bound of their confidence interval (38). Second-generation comparator tests fulfilling new international criteria would be used for validation of novel HPV DNA tests (39).*	
	≤ CIN1: 0.98 [c]	≤ CIN1: 0.99
	Annotation: *No disease is defined as absence of CIN2+ and includes women without histologically confirmed CIN2+ associated with one of the cHPV types (based on a standard target NAT).*	

Characteristic	Minimal	Preferred
Absolute clinical sensitivity	***Definition:*** *The ability of the HPV test under evaluation to test positive among women with underlying cervical disease, using histologically confirmed CIN2+ and/or CIN3+, associated with one of the cHPV types targeted by the test. Values do represent point estimates (40).*	
	CIN2+: 90% [d] CIN3+: 92% [d]	CIN2+: 95% CIN3+: 98%
Intra-laboratory reproducibility and inter-laboratory reproducibility	94%	98%
	Annotation: *The intra-laboratory and inter-laboratory reproducibility is expected to be assessed using international validated criteria (a set of ≥ 500 samples with 30% HPV-positive samples defined by a standard comparator test) (38,39). The TPPs targets are stricter than defined in current international validation guidelines since all currently clinically validated assays reach the minimal targets and most reach the preferred targets of 94% and 98% respectively (38).*	
Invalid/error rate	< 3%	< 1%
	Annotation: *This error rate should be validated under ideal circumstances to avoid "social invalids" due to human error. Other test characteristics, such as minimal operator steps or result display should help to minimize human error.*	
Time to result	< 4 hours (for manual assays, includes assay run time, excluding pre-analytical or extraction steps)	< 1.5 hours (for manual assays, includes assay run time, excluding pre-analytical or extraction steps)
	Annotation: *Pre-analytical activities include those conducted prior to performing the patient test (e.g. verifying the clinician's order), properly identifying the patient, patient preparation and collection of the sample.* *Note: The International Organization for Standardization (ISO) standard term is "preexamination", as per the Clinical and Laboratory Standards Institute (CLSI) Harmonized Terminology Database (https://htd.clsi.org/default.asp) (41).*	
Throughput (operator/work shift)	100 samples/work shift	400 samples/work shift
	Annotation: *Some instruments allow for running the assays overnight and providing the results the next day. For these, the minimal throughput is expected to be higher.*	

Characteristic	Minimal	Preferred
Design and operation		
Specimen stability/ transport	▪ **Dry sample:** Enable sample storage/transport between 2 °C and 30 °C for at least 15 days ▪ **Liquid sample:** Enable sample storage/transport between 2 °C and 30 °C for at least 30 days	▪ **Dry sample:** Enable sample storage/transport between 2 °C and 50 °C for at least 28 days ▪ **Liquid sample:** Enable sample storage/transport between 2 °C and 50 °C for at least 30 days
Specimen preparation	▪ All reagents that are required for specimen preparation are either supplied or listed ▪ Specimen preparation should involve minimal manual steps	▪ All reagents are ready to use or automated on-board sample preparation within assay
Steps performed by operator between specimen preparation and result [e]	Operationally simple manual steps associated with any required specimen preparation	Specimen can be transferred directly or is automatically transferred to the analyser without additional processing
Result display/ interpretation	Minimal operator interpretation of results	▪ Positive results with quantitative readout (cycle threshold [Ct] value, limit of detection [LoD] value, etc.) ▪ Automatic interpretation of results without operator interference
Additional consumables required but not provided within the test kit	Clear list of consumables that are required but not provided	Same as minimal
Conditions		
Training required	< 1-day on-site training	< 1-day online training
	Annotation: *This training refers to the HPV assay training and not to the use of the instrument. Instrument training should be done separately and should take sufficient time to ensure proper use of the full equipment, maintenance and troubleshooting, as applicable.*	
Operating conditions	▪ Between 15 °C and 35 °C at an altitude up to 4000 metres ▪ Both low and high humidity	▪ Between 10 °C and 50 °C at an altitude up to 4000 metres ▪ Both low and high humidity

Characteristic	Minimal	Preferred
Clean water	None	Same as minimal
Cold chain (for HPV test storage and transportation)	Cold chain acceptable	None required
Test kit stability from manufacturing and storage conditions	At least 18 months stable between 4 °C and 35 °C at 70% humidity and at 4000 metres altitude	At least 24 months stable between 4 °C and 50 °C at 90% humidity and at 4000 metres altitude
Test kit stability once opened/on-board stability (if applicable)	▪ 3 days at 4 °C ▪ 24 hours between 15 °C and 30 °C	▪ 14 days at 4 °C ▪ 7 days between 15 °C and 30 °C
Instrument maintenance	Where proprietary equipment used: ▪ routine maintenance included in procurement contract with replacement option ▪ daily preventive maintenance and/or calibration can be performed by lab-trained health worker ▪ invalid and error results provided with suggested corrective actions	Where proprietary equipment used: ▪ no maintenance required, swap out or replace ancillary device when needed ▪ weekly preventive maintenance can be performed by lab-trained health worker ▪ no calibration needed or can be performed remotely by central lab or manufacturer
Safety precautions	Closed, self-contained system	Same as minimal
Waste/disposal requirements	Standard biohazardous waste disposal or incineration	No requirements for incineration or biohazardous waste disposal

Characteristic	Minimal	Preferred
Quality and standards		
Internal quality control	The following controls should be internalized in the test for each individual test run: ▪ procedural control (e.g. amplification control, if applicable) ▪ sample adequacy control	Same as minimal and: ▪ positive/negative control
	Annotation: *The procedural control and the sample adequacy control can potentially be the same.*	
Quality management system	Compliant with ISO 13485 or equivalent	Certified ISO 13485 or equivalent
Data and connectivity		
Participant identification capability	Simple, self-contained way to digitally indicate: ▪ Participant identification number	Same as minimal
Data acquisition and display	Able to digitally store and view: ▪ participant identification number ▪ participant results Needs to consider privacy and data security laws	Same as minimal
Connectivity	Connection to internet	Connection to patient management systems

Characteristic	Minimal	Preferred
Data export	Remote export of encrypted data possible through universal serial bus (USB)	▪ Full data export (encrypted data only) can be done over mobile phone network (data transmission can automatically select between general packet radio service [GPRS] or more advanced networks and global system for mobile communication [GSM], based on available coverage). ▪ GPRS should be able to utilize the internet file transfer protocol (FTP) to transmit data: data transfer should be automatically initiated every 4–8 hours, checks to ensure that data are stored on the system until transferred/upload has been acknowledged. ▪ Data can be exported in a format compatible with Health Level Seven (HL7) standards, where appropriate; instrument tracks and transmits quality assurance data over time (such as identify shifts or trends). ▪ Need to consider privacy and data security laws.
Cost		
Cost per reportable result	< US$ 8	< US$ 5
	Annotation: *This should include the cost of the instrument, kits and all necessary consumables, including collection devices (including media as appropriate). This target price has been deliberated extensively in the TPP Development Group. Modelling of cost-effectiveness that was built into the secondary prevention guidelines updates in 2021 included the US$ 8.15 price in the cost-effectiveness calculations.*	

[a] Self-collection is not the same as self-testing. Samples may be self-collected, but HPV self-testing is currently not available.
[b] mRNA tests are currently only recommended for samples taken in the general female population by a health worker, but it is advised that any mRNA tests that are already available or forthcoming should also be validated for self-collection, as this is key for scaling up HPV screening programmes.
[c] Based on range of performance values from HPV tests that have been validated under VALGENT criteria, which uses specific comparator tests for this purpose *(38)*.
[d] Based on range of performance values from HPV tests that have been validated under VALGENT criteria *(38)* and Meijer et al.'s guidelines for carcinogenic HPV test requirements for primary screening *(38,40)*.
[e] Excluding sample collection.

Annex A2. TPP for HPV screening tests for use at the point of care

Characteristic	Minimal	Preferred
Scope		
Intended use	HPV screening for cervical pre-cancer and cancer detection	Same as minimal
Target population	Women and individuals with a cervix age 30 or older, and age 25 or older for those living with HIV	Same as minimal
Target use setting	Community (level 0) and level 1–2 health-care settings	Same as minimal
Specimen taker/ specimen type [a]	A test that is validated for ALL of the following: ▪ a **vaginal** sample self-collected by the participant ▪ a **vaginal** sample collected by a health worker (without speculum)	A test that is validated for ALL of the following: ▪ a **vaginal** sample self-collected by the participant ▪ a **vaginal** sample collected by a health worker (without speculum) ▪ a **cervical** sample collected by a health worker
	Annotation: *The collection of a vaginal sample (either by a health worker or by self-collection) does not require visualization of the cervix. The vaginal sample can be collected in the health facility, outreach settings with privacy or at home. The collection of a cervical sample requires exposing the cervix with a speculum, inserted by a health worker.*	
Specimen tester	A test that can be performed by a non-lab-trained health worker	Same as minimal; additionally, the test can be performed by a lay health worker

Characteristic	Minimal	Preferred
Technical specifications		
Target analyte type	Qualitative detection of HPV DNA or mRNA [b]	Same as minimal
	Annotation*: Aligning with the guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, these TPPs focus on HPV NATs, targeting HPV DNA or mRNA, as do most available tests and those in the pipeline. However, we do not discourage research on tests focusing on different targets. Any forthcoming guideline update will be reflected in this TPP.*	
Genotype spectrum	▪ 8 cHPV types: carcinogenic groups (most carcinogenic first) – 1a [16]; 1b [18, 45]; 1c [33, 58, 31, 52, 35] ▪ Probably (Group 2A) and possibly (Group 2B) carcinogenic types, including 68 and 66, should be excluded from screening tests	▪ 12 cHPV types: carcinogenic groups (most carcinogenic first) – 1a [16];1b [18, 45]; 1c [33, 58, 31, 52, 35]; 1d [59, 39, 51, 56] ▪ Probably (Group 2A) and possibly (Group 2B) carcinogenic types, including 68 and 66, should be excluded from screening tests
	Annotation*: Carcinogenic type groups 1a, 1b, 1c and 1d are adapted from the IARC colour-coded classification (https://publications.iarc.fr/604) (11) (see Table 1.2).*	
Result output/ target – individual genotyping	1-signal output positive/negative pooled (excluding control/invalid)	At least 2-signal output (excluding control/invalid and/or negative): 1. Carcinogenic group 1a [16] individually; or grouped with group 1b [18, 45] pooled or individual 2. Carcinogenic group 1c [33, 58, 31, 52, 35] and carcinogenic group 1d [59, 39, 51, 56] pooled
	Annotation 1*: HPV45 may be pooled with either HPV18 or carcinogenic group 1c [33, 58, 31, 52, 35] signal output.* ***Annotation 2****: Aligning with the guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, screen and treat algorithms with or without triage are recommended for women from the general population; for women living with HIV, only screen, triage and treat algorithms are recommended. This triage can be done using HPV-limited genotyping, colposcopy, VIA or cytology.*	
Test kit format	Assay in which reagents for sample preparation (including nucleic acid extraction, if applicable), amplification and detection are all included. The test may be run on a small instrument or be instrument-free.[c]	Same as minimal

Characteristic	Minimal	Preferred
Instrument for sample analysis	If the test requires an instrument, it should be: ▪ lightweight ▪ portable ▪ shock-proof ▪ sturdy	If the test requires an instrument, it should be: ▪ lightweight ▪ handheld ▪ portable ▪ shock-proof ▪ sturdy ▪ capable of multi-disease testing
Need for additional equipment	No additional equipment should be needed (excluding consumables), however, mobile phones may be considered for result read-out and data capture, as well as inexpensive equipment such as heating blocks	No additional equipment should be needed (excluding consumables), however, mobile phones may be considered for result read-out and data capture
Performance		
Cross-reactivity	Assay should not cross-react with: ▪ other common non-HPV microorganisms that can infect the genital tract ▪ non-targeted phylogenetically related HPV genotypes < 2%	Assay should not cross-react with: ▪ other common non-HPV microorganisms that can infect the genital tract ▪ non-targeted phylogenetically related HPV genotypes < 1%
Interference	Assay performance should not be impacted by common interfering substances present in female genital tract	Same as minimal
Relative clinical sensitivity	***Definition****: The ability of the HPV test under evaluation to test positive among women with underlying cervical disease, using histologically confirmed CIN2+ and/or CIN3+, associated with one of the cHPV types targeted by the test, compared to same ability of a comparator HPV test. Values do not represent point estimates, but the lower bound of their confidence interval (38). Second-generation comparator tests fulfilling new international criteria would be used for validation of novel HPV DNA tests (39).*	
	CIN2+: 0.90 [d] CIN3+: 0.95 [d]	CIN2+: 0.95 CIN3+: 0.98

Characteristic	Minimal	Preferred
	***Annotation**: This TPP will be updated in five years or earlier if current tests in the pipeline are developed and go through validation. If new POC tests can substantially increase screening uptake compared to current tests, more flexible criteria for test performance may be considered as long as these tests are applied to populations for which there is enough certainty that they will attend regular screening, or the next screening round provided according to local context.*	
Relative clinical specificity	***Definition**: The ability of the HPV test under evaluation to test negative among women without underlying clinically significant cervical disease, compared to the same ability of a comparator HPV test. Values do not represent point estimates, but the lower bound of their confidence interval (38). Second-generation comparator tests fulfilling new international criteria would be used for validation of novel HPV DNA tests (39).*	
	≤ CIN1: 0.98 [d]	≤ CIN1: 0.99
	***Annotation**: No disease is defined as absence of CIN2+ and includes women without histologically confirmed CIN2+ associated with one of the cHPV types (based on a standard target NAT).*	
Absolute clinical sensitivity	***Definition**: The ability of the HPV test under evaluation to test positive among women with underlying cervical disease, using histologically confirmed CIN2+ and/or CIN3+, associated with one of the cHPV types targeted by the test. Values do represent point estimates (40).*	
	CIN2+: 90% [e] CIN3+: 92% [e]	CIN2+: 95% CIN3+: 98%
Invalid/error rate	< 3%	< 1%
	***Annotation**: This error rate should be validated under ideal circumstances to avoid "social invalids", due to human error. Other test characteristics, such as minimal operator steps or result display, should help to minimize human error.*	
Time to result	< 1 hour (for manual assays, includes assay run time, excluding pre-analytical or extraction steps)	< 30 minutes (for manual assays, includes assay run time, excluding pre-analytical or extraction steps)
	***Annotation**: Pre-analytical activities include those conducted prior to performing the patient test (e.g. verifying the clinician's order), properly identifying the patient, patient preparation and collection of the sample.* *Note: The International Organization for Standardization (ISO) standard term is "preexamination", as per the Clinical and Laboratory Standards Institute (CLSI) Harmonized Terminology Database (https://htd.clsi.org/default.asp) (41).*	

Characteristic	Minimal	Preferred
Design and operation		
Specimen stability	Dry OR liquid sample: enable sample storage between 2 °C and 45 °C for at least 7 days	Dry sample only: enable sample storage between 2 °C and 50 °C for at least 7 days
Specimen preparation	All reagents are ready to use or automated on-board sample preparation within assay	Same as minimal
Steps performed during sample testing by health worker until result output	Specimen does not need more than three simple operator steps before transfer to analyser (excluding pre-analytical activities)	Specimen can be transferred directly or is automatically transferred to the analyser without additional processing
	*Please refer to the **annotation** above in the row for "Time to result" (41).*	
Result display/ interpretation	Result can be read with the naked eye with minimal instructions for interpretation required by user, or with an integrated reader or mobile phone application with an easy pictorial display for each result output	Same as minimal
Stability of valid result	At least 30 minutes (after which results may be false or invalid)	A valid result does not change once determined
	***Annotation**: There should be clear language in the instructions for use regarding test reading.*	
Additional consumables required but not provided within the test kit	None, other than for specimen collection, or fixed-volume pipettes for transfer	Same as minimal
Conditions		
Training required	< 2 hours online training	< 30 minutes online training
Operating conditions	▪ Between 4 °C and 45 °C at an altitude up to 4000 metres ▪ Both low and high humidity	Same as minimal

Characteristic	Minimal	Preferred
Clean water	None required	Same as minimal
Cold chain	None required	Same as minimal
Power	▪ If power is needed for an instrument-free test, it should be compatible with a portable external power source ▪ If the test requires an instrument, it should be compatible with a portable external power source or have an integrated or external rechargeable battery	▪ For an instrument-free test, no power required ▪ If the test includes an instrument, it should have an integrated rechargeable battery or work with commercially available rechargeable batteries
Test kit stability from manufacturing and storage conditions	At least 18 months stable between 4 °C and 35 °C at 70% humidity and at 4000 metres altitude	At least 24 months stable between 4 °C and 50 °C at 90% humidity and at 4000 metres altitude
Test kit stability once opened/on-board stability (if applicable)	3 days at room temperature	7 days at room temperature
Instrument maintenance	If the test requires an instrument: ▪ no regular maintenance required ▪ preventive measures can be performed by non-trained laboratory staff if needed, following instructions for use ▪ no calibration needed or can be performed remotely by central lab or manufacturer	Same as minimal
Safety precautions	Closed, self-contained system; unprocessed sample transfer only; no open handling of biohazardous material	Same as minimal
Waste/disposal requirements	▪ Standard biohazardous waste disposal or incineration ▪ No high temperature incineration required ▪ Small environmental footprint	▪ Standard biohazardous waste disposal ▪ No incineration required ▪ Small environmental footprint ▪ Compostable plastics for test and other materials after decontamination

Characteristic	Minimal	Preferred
Quality and standards		
Internal quality control	The following controls should be internalized in the test for each individual test run: ▪ procedural control (e.g. amplification control if applicable) ▪ sample adequacy control	Same as minimal
	***Annotation**: The procedural control and the sample adequacy control can potentially be the same.*	
Quality management system	Compliant with ISO 13485 or equivalent	Certified ISO 13485 or equivalent
Data and connectivity		
Participant identification capability	Space to manually or digitally record participant identification number	Simple, self-contained way to digitally indicate participant identification number
Digital data acquisition and display	No data acquisition or display	Able to digitally store and view participant identification number and test results; need to consider privacy and data security laws
Connectivity	None required	Connection to internet and/or patient management systems, or ability to send results to patients or health workers as appropriate. This may be done indirectly for instrument-free tests via freely available mobile phone apps. Need to consider privacy and data security laws.

Characteristic	Minimal	Preferred
Data export	None required	If technology allows: ▪ Full data export (encrypted data only) can be done over mobile phone network (data transmission can automatically select between general packet radio service [GPRS] or more advanced networks and global system for mobile communication [GSM], based on available coverage). ▪ GPRS should be able to utilize the internet FTP to transmit data; data transfer should be initiated every 4–8 hours, with checks to ensure that data are stored on the system until transferred/upload has been acknowledged. ▪ Data can be exported in a format compatible with Health Level Seven (HL7) standards, where appropriate; the instrument tracks and transmits quality assurance data over time (such as identify shifts or trends). ▪ Need to consider privacy and data security laws.
Cost		
Cost per reportable result	< US$ 8	< US$ 3
	Annotation: *This should include the cost of the instrument (if applicable), kits and all necessary consumables, including collection devices (and including media as appropriate). This target price has been deliberated extensively in the TPP Development Group. No cost-effectiveness or affordability studies of HPV POC tests are available to underpin these targets. However, they are based on agreement by the TPP Development Group after considering cost estimations of promising POC technologies under development retrieved from peer-reviewed articles and available price setting in tenders for procurement of laboratory HPV tests.*	

[a] Self-collection is not the same as self-testing. Samples may be self-collected, but HPV self-testing is currently not available.
[b] mRNA tests are currently only recommended for samples taken in the general female population by a health worker, but it is advised that any mRNA tests that are already available or forthcoming should also be validated for self-collection, as this is key for scaling up HPV screening programmes.
[c] While few tests for use at the POC are available on the market, there are various HPV POC tests in the pipeline. Both instrument-free and device-based POC tests align with the proposed TPPs, with applications depending on the local context and the specific characteristics of marketed products. Ease of use, reduced equipment management requirements and portability of instrument-free tests may be countered with better performance, higher throughput and fewer waste disposal requirements of tests that use a small instrument. Other characteristics including cost, time to result, and ancillary consumable requirements will be largely product-dependent and could be considered during product selection. A mix of different marketed products capable of providing results at the POC will be needed to fit into different country contexts. The TPP aims to provide guidance for developers to ensure innovations will increase access to quality screening.
[d] Based on range of performance values from HPV tests that have been validated under VALGENT criteria, which uses specific comparator tests for this purpose *(38)*.
[e] Based on range of performance values from HPV tests that have been validated under VALGENT criteria and Meijer et al.'s guidelines for carcinogenic HPV test requirements for primary screening *(38,40)*.