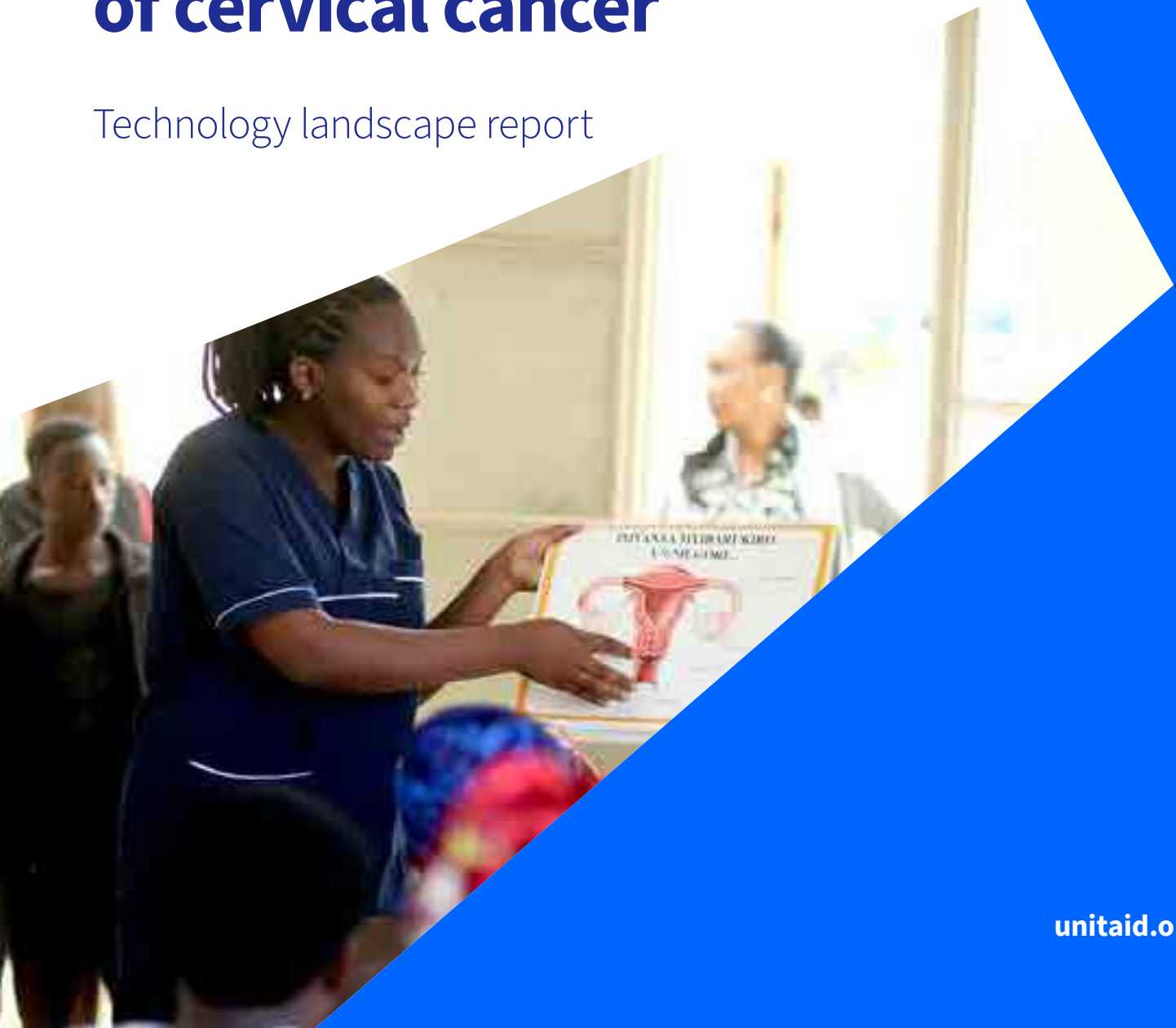
Unitaid
SAVE LIVES FASTER

Screening and treatment of precancerous lesions for secondary prevention of cervical cancer

Technology landscape report



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Content

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Conflicts of interest

KC's research is funded by the National Health and Medical Research Council (NHMRC) of Australia (Fellowship APP1194679, Centre of Research Excellence in Cervical Cancer Control 1135172). KC and MS are co-PIs of an investigator-initiated trial of cervical screening, Compass, run by the Australian Centre for Prevention of Cervical Cancer (ACPCC), which is a government-funded not-for-profit charity; the ACPCC has received equipment and a funding contribution from Roche Molecular Diagnostics, and operational support from the Australian Government. KC and MS are also co-leads on a major investigator-initiated implementation program Elimination of Cervical Cancer in the Western Pacific (ECCWP) which will receive support from the Minderoo Foundation and equipment donations from Cepheid Inc. KC worked for Polartechnics (now TruScreen) in the period 1996-2005, prior to commencing her research career. MS is also a trustee on the ROSE Foundation Board. The ROSE Foundation receives donation income to support in country activities, including the purchase of laboratory consumables for HPV testing. MS's employer, ACPCC, does not receive revenue from the ROSE Foundation.

Glossary of terms

AI	artificial intelligence
AVE	automated visual evaluation
CE-IVD	Conformité Européenne, In Vitro Diagnostics
CIN	cervical intraepithelial neoplasia
DNA	deoxyribonucleic acid
FDA	U.S. Food and Drug Administration
HCW	health care worker
HIC	high-income country
HIV	human immunodeficiency virus
HPV	human papillomavirus
hrHPV	high-risk human papillomavirus
IARC	International Agency for Research on Cancer
IFU	instructions for use
IVD	in vitro diagnostics
LBC	liquid-based cytology
LEEP	loop electrosurgical excision procedure
LLETZ	large loop excision of the transformation zone
LMICs	low- and middle-income countries
mRNA	messenger ribonucleic acid
NAAT	nucleic acid amplification test
NCI	National Cancer Institute
NGO	nongovernmental organization
PCR	polymerase chain reaction
POC	point of care
RNA	ribonucleic acid
RFI	request for information
SHI	Social Health Insurance
SRA	Stringent Regulatory Authority
TA	thermal ablation
TB	tuberculosis
TPP	target product profiles
VIA	visual inspection with acetic acid
WHO	World Health Organization
WHO-PQ	World Health Organization Prequalification

Executive summary

Unitaid is a global health agency dedicated to finding innovative solutions to prevent, diagnose, and treat diseases more quickly, cheaply, and effectively in low- and middle-income countries (LMICs). Hosted by the World Health Organization (WHO), Unitaid addresses one of the biggest challenges in health innovation: closing the gap between the late-stage development of health products and their widespread adoption at scale. Since 2018, Unitaid has invested in programs that focus on introducing innovative tools for the secondary prevention of cervical cancer.

Cervical cancer, caused by an infection with the human papillomavirus (HPV), is one of the most preventable and treatable cancers, yet it remains a leading cause of female mortality worldwide, disproportionately affecting LMICs. This disparity is partly due to a historical lack of access to cervical screening and cancer treatment facilities, as well as the higher percentage of women living with HIV in these regions, who are highly vulnerable to HPV co-infection and at greater risk of progression to cervical cancer. Given these disparities, there is an urgent need for accelerated introduction and adoption of effective, affordable cervical cancer screening and treatment technologies in LMICs.

In 2020, WHO launched the **Global Strategy to Accelerate the Elimination of Cervical Cancer**, a comprehensive, population-based approach aimed at eliminating cervical cancer by 2030. This strategy supports scaling up across the three pillars of prevention: vaccination, screening and precancer treatment, and cancer treatment. Even with the introduction of the HPV prophylactic vaccine, access to efficient screening and precancer treatment programs will remain critical for several decades to identify precancer and cervical cancer cases among both unvaccinated women and younger vaccinated cohorts.

Over the past decade, technological innovation has transformed cervical cancer prevention. WHO's 2021 guidelines for cervical cancer screening and treatment of precancerous lesions recommend HPV DNA testing as the most effective and cost-efficient tool for primary cervical screening. This surpasses previous alternatives such as visual inspection with acetic acid (VIA) and cytological methods, including the Pap smear and liquid-based cytology (LBC). In the 2021 guidelines, VIA, Pap smear and LBC are recommended as triage tools within a screen-triage-and-treat pathway, essential for women living with HIV and optional for the general population (in addition to screen-and-treat).

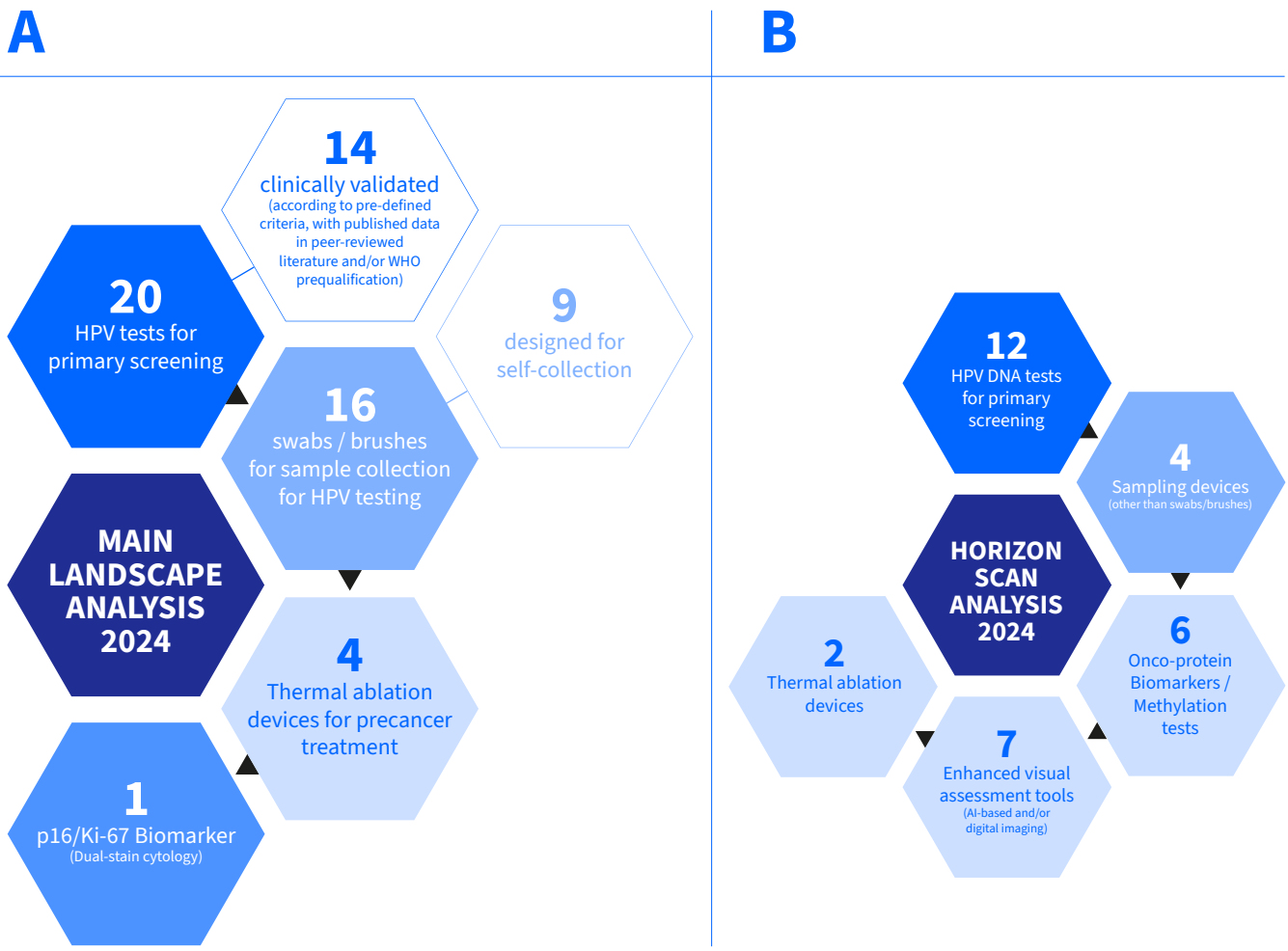
The objective of this landscape review is to provide an overview of technologies for the secondary prevention of cervical cancer, focusing on screening, diagnosis and treatment of pre-cancerous lesions. It identifies critical technological and access barriers to managing the disease at the precancer stage. The review focuses on technologies particularly suited to LMIC settings. While comprehensive, this report does not provide an exhaustive list of all available products. An evidence- and expert-informed inclusion criteria process was applied for each technology category (see Section 2: Summary of Methods). In the current landscape (2024), the following technologies have been identified (Figure 1A - main lanscape analysis):

- 20 HPV tests (19 HPV DNA and 1 HPV mRNA tests) for primary screening, of which 14 are clinically validated (based on pre-defined criteria) with published data in peer-reviewed literature and/or WHO prequalified. Additionally, 17 tests can perform partial genotyping (HPV 16 and 18) for triage.
- 16 swabs or brushes for sample collection, 9 of which are designed for self-collection.
- 4 thermal ablation devices for precancer treatment.
- 1 dual-stain cytology test.

A horizon scan was also performed, identifying a range of emerging products and technologies for HPV testing, triage and treatment, which were evaluated based on pre-defined criteria (see Section 2: Summary of Methods). Manufacturers were identified following extensive consultation with key stakeholders and an open request for information (RFI) from Unitaid. Only products with direct information submitted by suppliers were included.

It is important to acknowledge that this landscape primarily reflects information provided by manufacturers and suppliers at a specific point in time, which was then supplemented by further research.

Figure 1
Summary of the products/technologies included in the Unitaid technology landscape for screening and treatment of precancerous lesions for secondary prevention of cervical cancer



1.
Introduction

1.1 The burden of cervical cancer

Cervical cancer is one of the most preventable and curable forms of cancer when detected and treated early. Despite this, cervical cancer remains one of the leading causes of cancer death in women worldwide, with an estimated 662,301 new cases and 348,874 deaths in 2022. [1, 2] Worldwide, cervical cancer was cervical cancer was the 4th leading cause of cancer in women of all ages, and in women < 45 years, it was the second most common cancer [1, 2].

A highly disproportionate burden of these cases (90%) falls on women living in low- and middle-income (including lower-middle and upper-middle-income) countries (Figure 2) [1]. This inequity is largely due to a long-standing lack of access to high-quality screening and cancer treatment options within these countries [3, 4].

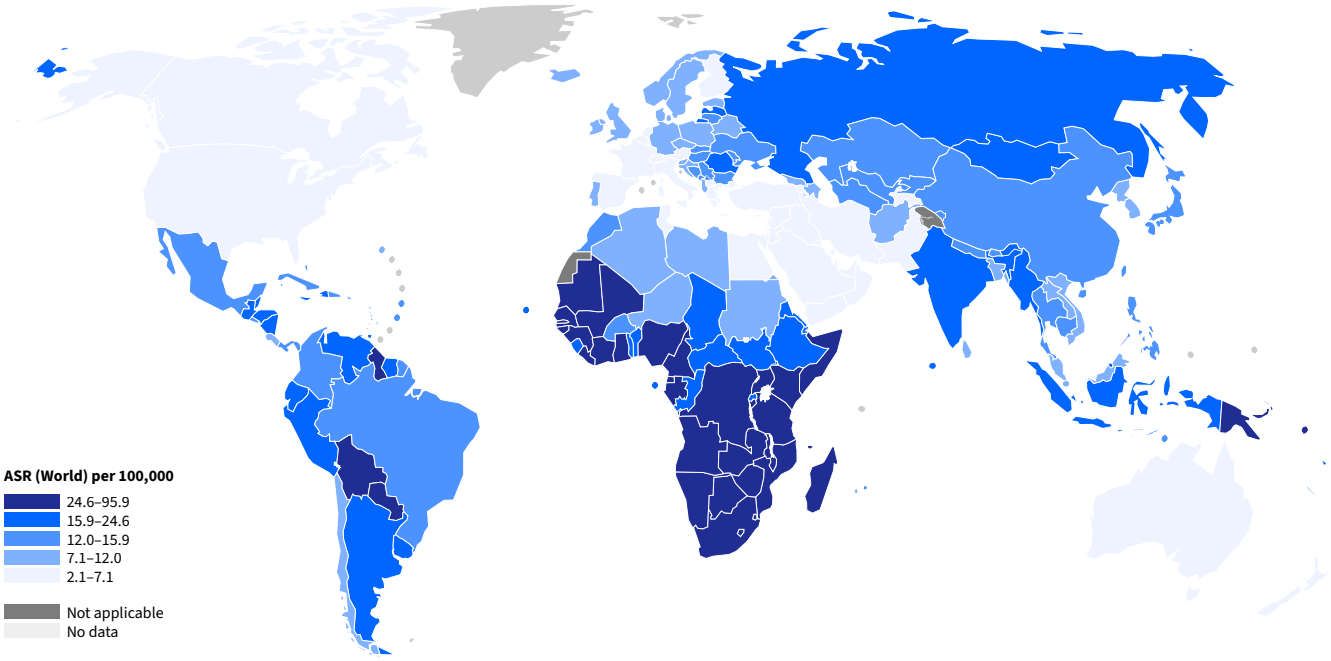
Almost all cases of cervical precancer and cancer are caused by an HPV infection. There are more than 200 HPV genotypes [5]. Twelve are classified by the International Agency for Research on Cancer (IARC) as carcinogenetic to humans (HPV 16, 18, 33, 31, 35, 39, 45, 51, 52, 56, 58 and 59) and considered as high-risk HPV genotypes (hrHPV); and one as probably carcinogenic (HPV 68) [6]. The highest-risk genotypes, 16 and 18, are responsible for approximately 70% of all cervical cancer cases globally. Although most HPV infections clear naturally, and many precancerous lesions resolve spontaneously, chronic HPV infection can progress to invasive cervical cancer if left undetected and untreated [7].

When considering target populations for screening, WHO distinguishes women living with HIV from the general population of women. HPV is a threat particularly to the health of women living with HIV, as they are less likely to clear HPV and are six times more likely to develop cervical cancer once infected with HPV when compared with HIV-negative women [8]. Evidence shows that HIV-HPV co-infected women develop cervical cancer at ages up to 15 years earlier than HIV-negative women [9]. Among women living with HIV, hrHPV prevalence rates are higher than in the general population, reaching levels higher than 75%, for example in Uganda . This combination of a higher rate of HPV infection, a higher risk of faster progression from infection to invasive cervical cancer if pre-invasive lesions are left untreated, and the lack of access to lifesaving prevention and treatment services imposes a higher burden on women living with HIV, in settings where the health needs are highest [3].

662,301
new cases of cancer in women worldwide

348,874
deaths in 2022

Figure 2
Geographical distribution of cervical cancer incidence rates in 2022



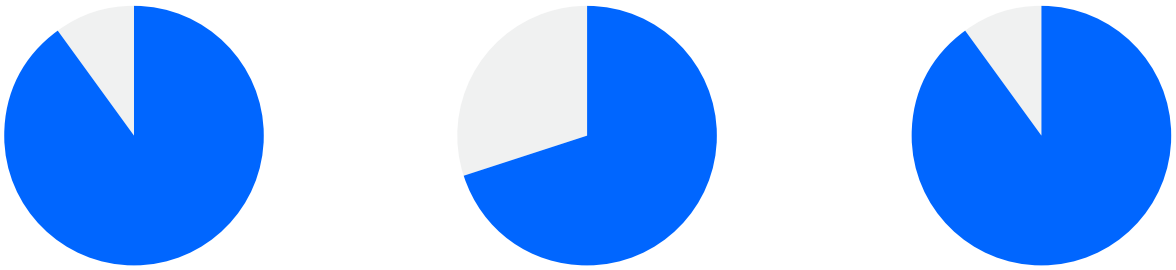
Source: Global Cancer Observatory-IARC,2022.

1.2 The response to the global CxCa burden

In response to the high burden of cervical cancer incidence and mortality, WHO launched the *Global Strategy to Accelerate the Elimination of Cervical Cancer as a public health problem;* a comprehensive, population-based approach to accelerate globally the elimination[1] of cervical cancer (hereafter referred to as WHO's cervical cancer elimination strategy) [3]. This strategy aims to put all countries on the path to elimination within the century, proposing global targets for three pillars: vaccination, screening and treatment (Figure 3).

1 The elimination threshold is defined as a rate of cervical cancer incidence lower than 4 per 100,000 woman-year (when cervical cancer incidence rates are age-standardised using the World 2015 population).

Figure 3
Three pillars 90-70-90 targets, to be met by 2030 (Source: WHO Global Strategy to accelerate the elimination of cervical cancer as a public health problem, 2020)



90%

of girls fully vaccinated with HPV vaccine by age 15 years.

70%

of women are screened with a high-performance test by 35 years of age and again by 45 years of age.

90%

of women identified with cervical disease receive treatment (90% of women with precancer treated, and 90% of women with invasive cancer managed).

Modelling to inform the WHO's cervical cancer elimination strategy predicted more than 74 million cervical cancer cases and 62 million cervical cancer deaths could be prevented by 2120 [11], while investing in the elimination targets could return US$3.20 to the economy for every dollar invested through 2050, rising to US$26 when societal benefits are incorporated [3]. To achieve elimination in the shortest timeframe and with maximum impact, interventions to meet these three targets should be implemented simultaneously and at scale, with focused action across the continuum of care.

To support WHO's cervical cancer elimination strategy, WHO released an updated guideline for cervical cancer screening and treatment of cervical precancer lesions for cervical cancer prevention (second edition, 2021), hereafter referred to as WHO 2021 guidelines. These WHO 2021 guidelines are produced as living guidelines, continuously reviewed as technology and evidence evolves [2]. In May 2023, during the 76th World Health Assembly, WHO reaffirmed the commitment to pursue the elimination of cervical cancer as a public health problem and launched the WHO Cervical Cancer Elimination Initiative: From Call to Action to Global Movement.

1.2.1 Prophylactic HPV vaccination

Prophylactic HPV vaccination provides primary prevention against invasive cervical cancer and other HPV-related cancers. It has shown consistently very high levels of protection (approaching 98-100%) against new infection with vaccine-included types in individuals who have not been exposed to those HPV types [12, 13].

Since December 2022, WHO recommends that countries can now choose a one- or two-dose schedule for 9–14-year-old girls and young women aged 15-20, as evidence suggests that the single-dose option provides comparable high levels of individual protection. From a public health perspective, this option can offer substantial benefits, being more efficient, less resource-intensive and easier to implement . One-dose vaccination has already been adopted as a policy recommendation across multiple countries and regions.

1.2.2 Cervical cancer screening and treatment of precancerous lesions

Secondary prevention remains essential for these cohorts of adult women who did not have access to HPV prophylactic vaccines as adolescents and this will remain the case for many years into the future .

Cervical cancer screening and treatment of precancerous lesions identifies asymptomatic women at risk of developing cervical cancer and provides early treatment at the precancer stage [3]. This secondary prevention strategy has dramatically decreased the incidence and mortality of cervical cancer in settings with long-standing effective screening programs, such as Australia, the USA and many European countries [1]. WHO recommends using HPV testing as the primary screening test rather than VIA or cytology. HPV-based screening in a screen-and-treat or screen-triage-and-treat approach, with a screening interval of every 5 to 10 years, is currently recommended among the general population of women aged 30 to 49 years and is recommended every 3 to 5 years in a screen-triage-and-treat approach for women living with HIV [2].

Primary screening

In 2021, WHO proposed major changes in cervical screening and treatment, recommending 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[2] [1]. A 2021 review of the evidence by IARC found that “although several methods currently used in screening are effective in reducing the incidence of and the mortality associated with cervical cancer, HPV testing alone is the most effective given its balance of benefits and harms” [17].

For countries that have yet to establish a routine screening program, the WHO advises that programs be initiated with HPV testing. Countries with existing programs utilizing quality-assured cytology as the primary screening test should continue doing so until HPV testing is operational. Countries with existing programs using VIA as the screening test should transition rapidly as financial and operational conditions allow due to the high variability of performance of VIA and inherent challenges with its quality assurance. Specific recommendations are detailed further in the WHO 2021 guidelines [2, 18]. HPV testing is an extensively proven screening method, which prevents more cervical cancers and saves more lives when compared to VIA or cytology as a primary screening test [19]. Table 1 summarizes the main characteristics of primary cervical screening tests.

2 At the time of the publication of this landscape, WHO did not recommend the use of HPV mRNA test in women living with HIV, with an intention to review the growing body of evidence of performance of this test in women living with HIV through the living guidelines review process.

Table 1
Selected characteristics of different primary cervical screening tests

	HPV DNA	HPV mRNA	Cytology	Visual inspection with acetic acid (VIA)	AI-based tools
Recommended in WHO 2021 guidelines	Preferred primary test, for both general population and women living with HIV [1]	Alternative primary test for general population [2] Not recommended for women living with HIV	Quality-assured cytology should continue until HPV testing is operational [1]	VIA programs should transition rapidly to HPV testing [1]	Not recommended. *Under evaluation – will be covered in a future version of WHO living guidelines*
Performance variability	Low	Low	High	High	Under evaluation
Screening Interval	General Pop: 5-10 y women living with HIV: 3-5 y	General Pop: 5 y women living with HIV: Not rec.	3 y	3 y	Under evaluation
Capacity for single-visit approach to screen (+/-triage) and treat	Variable – may be high with POC	Low – no POC currently available	Low	High	High
Compatibility with self-care (avoid speculum examination)	Yes	Compatible, but with lower performance [3]	No	No	No
Cost-effectiveness ($/HALY saved)	High	High	Low	Low (Moderate – if high sensitivity)	Under evaluation/ unknown at scale

(1) Strong recommendation, moderate-certainty evidence; (2) Conditional recommendation, moderate-certainty evidence
(3) Available data suggest that HPV mRNA testing is associated with a performance degradation with self-collected samples
HALY - Health-Adjusted Life Years; HPV – Human Papilloma Virus; POC – point-of-care; VIA – visual inspection with acetic acid; WHO – World Health Organization; women living with HIV – women living with HIV
Source: WHO 2021-2022 guidelines, including Web Annex A: Syntheses of evidence and Web Annex B: Evidence to Decision Tables

The WHO recognizes that transitioning from VIA or cytology to HPV testing may be challenging from a financial and operational perspective, particularly for LMICs [1]. While the cost of HPV testing is greater than VIA, HPV testing is the most cost-effective cervical cancer screening approach for LMICs due to its higher sensitivity for precancer (CIN2+ and CIN3+) and superior negative predictive value compared to other screening methods [2, 19-21]. This allows screening intervals to be safely extended among women in whom HPV is not detected, which increases the cost-effectiveness at the whole-of-population level.

A transitional period may require new laboratory infrastructure, including sample transportation and result return networks, as well as well-trained technicians due to the more complex infrastructure and workforce requirements associated with HPV testing compared with VIA. However, as transitions to self-collected samples and point-of-care (POC) molecular diagnostics (once available on the market) occur, infrastructure costs are expected to decrease, as HPV testing will require less differentiated personnel and allow task-shifting. As an example, with self-sampling, health care professionals will no longer need to do routine pelvic examinations and will be able to allocate their time and skills to other activities, such as the assessment and treatment of women in whom HPV is detected and follow-up of previously treated women. Another important consideration is the possibility of utilizing test platforms that were installed for other disease needs, like HIV, tuberculosis (TB) or COVID-19 testing.

Triage testing

In the WHO 2021 guidelines, the cervical 'screen and treat' method is one possible option for the general population of women. An additional step of triage testing before treatment, as a part of a 'test, triage and treat' approach, is recommended for both women living with HIV and as an alternative approach for the general population of women. This additional triage step may be used in settings where resources are available to improve the balance of benefits to harms by reducing overtreatment rates [22, 23]. While the benefits, harms and programmatic costs of triage options seem to be reasonably similar when considered over the long term and while the choice of method should rely on feasibility, training, program quality assurance and resources in countries [2], it is also important to consider the main characteristics of each method. See WHO 2021 guidelines for specific 'screen, triage and treat' algorithms.

Triage tests currently available and recommended include: hrHPV partial genotyping tests, conventional cytology, LBC, colposcopy that may or may not include biopsy for histological diagnosis, VIA and more recently, dual-stain cytology for general population[3]. Some of these triage tests may be conducted sequentially, such as cytology followed by colposcopy with biopsy. This is particularly a common approach in relatively high-resource settings. Common triage techniques such as VIA or colposcopy are based on visual assessment of the cervix and can have more variable accuracy, as they depend upon the subjective interpretation of a clinician [24-26], though performance seems to improve when examiners know that HPV has been detected. The ESTAMPA trial used VIA as triage of HPV-positive women across different countries in Latin America and had a global sensitivity of 82% for CIN2+, although with high variability between examiners (sensitivity range: 25%-95% and specificity range: 45-94%) [27].

While not currently recommended by WHO, other tests have been introduced that may be viable options for triage including: HPV biomarker tests, including oncoprotein detection or DNA methylation, digital colposcopy and other visual inspection tests, based on artificial intelligence (AI) / machine-learning platforms (e.g., automated visual evaluation (AVE) of digital images) [2].

Note that there is a distinction between 'triage' and using visual evaluation (VIA) to assess eligibility for ablative treatment. In the latter case, when women have an indication for ablative treatment, there should be an evaluation before the procedure to determine treatment eligibility by identifying the transformation zone type and the location and size of the lesion (if visible). If not eligible, women should be referred for excisional treatment or further evaluation.

3 Dual-stain cytology is not recommended for use in women living with HIV because evidence on the outcomes of using dual-stain cytology applicable to this population was minimal – WHO dual-stain cytology guidelines

1.3 Unitaid and its leadership in expanding access to cervical cancer prevention

Unitaid is a global health agency hosted by WHO, dedicated to finding innovative solutions to prevent, diagnose and treat global diseases quickly, cheaply and effectively in LMICs. Unitaid occupies a unique place in global health, championing equitable access to health tools and ensuring that innovative health solutions are fit-for-purpose, affordable and rapidly available for people and communities who need them most.

Since 2018, Unitaid has publicly committed to supporting WHO's cervical cancer elimination strategy. This commitment reflects Unitaid's vision of expanding access to critical health products and services for those most in need via three strategic objectives: to accelerate the introduction of quality health products, to create systemic conditions for sustainable and equitable access to health services and to foster inclusive and demand-driven partnerships for innovation.

With US$81 million invested over the last five years (Figure 4), Unitaid has been the largest funder of innovative tools to detect and treat precancerous lesions in women living in low-resource settings, who might not have access to vaccination and are most at risk [28]. In collaboration with global health partners and national governments, Unitaid has helped LMICs progress towards elimination through an integrated prevention program that has already screened 1.5 million women in 14 different countries and treated more than 87% of eligible women who were identified with precancer.

Figure 4
Unitaid major global achievements in cervical cancer screening (results as of December 2023)

Unitaid investment* across 14 countries since 2019	1. INTEGRATED SERVICE DELIVERY FOR CERVICAL CANCER SCREENING AND TREATMENT	2. IMPROVED ACCESSIBILITY OF OPTIMAL TOOLS	3. RESULTS ACROSS THE 14 COUNTRIES
14 **Countries supported through CHAI (10 countries**) and Expertise France led SUCCESS Consortium (4 countries***), as well as global WHO enabler grant** *$81M since 2019; **India, Kenya, Malawi, Nigeria, Rwanda, Senegal, South Africa, Uganda, Zambia, Zimbabwe ***Burkina Faso, Côte d'Ivoire, Guatemala, and the Philippines, with four additional countries supported by the French government with 5M€ since 2024	**1,000+** Sites across 14 countries providing integrated service delivery with routine health services incl. HIV, family planning and maternal and child health. *Screening with HPV testing inc. self-sampling & treatment with thermal ablation introduced **11,400+** Healthcare workers including nurses, midwives, community health workers trained across 14 countries *Supportive supervision and mentorship instituted within ministries of health structures	**40%↓** Reduction in HPV test price (median). Current price is <US$9.00 per test from 3 of 4 suppliers. **45%↓** Reduction in thermal ablation device price ceiling. Current average price* of Liger and Wisap devices is ~US$932. *Liger HTU110 US$925, Wisap C3ECO4 €870 **12 out of 14** Program countries have endorsed HPV testing in national screening guidelines Burkina Faso, Cote d'Ivoire, Guatemala, Kenya, Malawi, Nigeria, Philippines, Rwanda, Senegal, Uganda, Zambia, Zimbabwe **6,000+** Thermal ablation devices deployed in ~30 countries across Africa, Asia and Latin America. ~50% placed at primary health facilities, decentralizing treatment access **Scalability** Supporting ministries of health define national screening and treatmen targets; build costed national scale up plans	**~1.5 million** women screened, with ~530,000 screened with HPV tests (>50% with self-sampling) **>87%** Of eligible women identified with pre-cancerous lesions treated **81%** Of women referred for invasive cancer attended referral visit

Unitaid's US$41 million grant to the Clinton Health Access Initiative (CHAI) has helped deploy innovative screening tools and introduce new portable devices for treatment. This project (2019-2025) has also proven out a range of delivery models for cervical screening.

Simultaneously, Unitaid's SUCCESS (Scale Up Cervical Cancer Elimination with Secondary Prevention Strategy) project (2019-2024), led by Expertise France and implemented in partnership with Jhpiego and the Union for International Cancer Control (UICC), is helping develop screening and precancer treatment capacity across Burkina Faso, Cote d'Ivoire, Guatemala and the Philippines. Building on existing experiences in four project countries, SUCCESS has introduced HPV testing with self-collection and treatment with thermal ablation [29, 30]. These services are adapted to the specific context of each country and integrated into a variety of public health care settings that provide care for people living with HIV, sexual and reproductive health support and family planning services [30].

By the end of December 2023, Unitaid has supported screening of more than 1,500,000 women, including 530,000 with primary HPV testing, across 14 different countries. The major achievements are described in Figure 4. Unitaid-supported programs give more women access to screening and treatment and

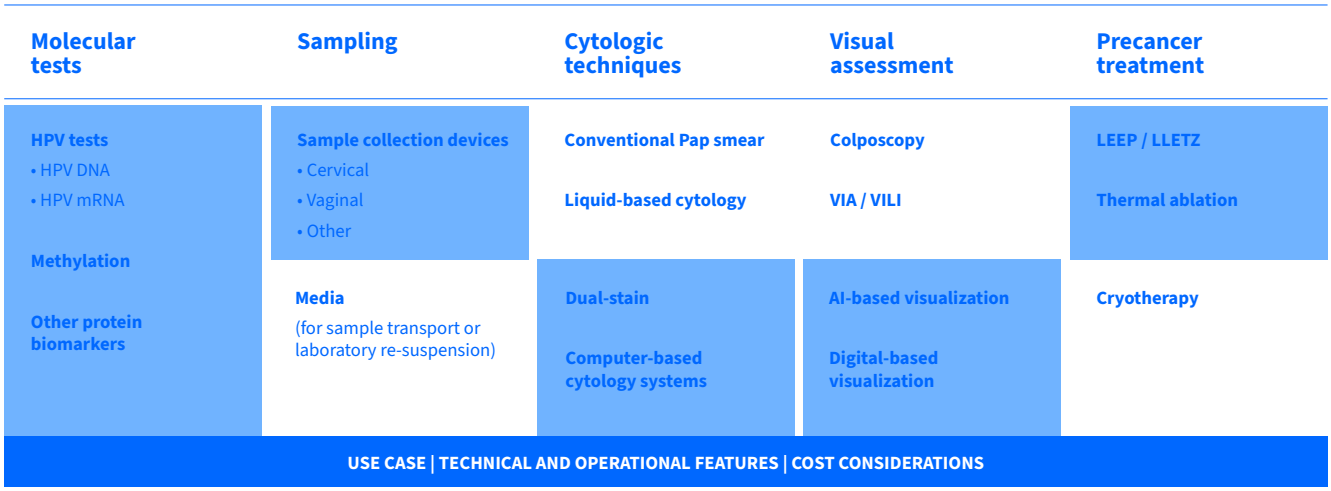
are helping embed a sustainable approach to cervical cancer prevention in national health systems [28].

In addition, since 2020, Unitaid has been providing financial support to WHO's Cervical Cancer Elimination Initiative, enabling their critical work in championing the elimination agenda.

Scope of this review

While efforts to scale up the three cervical cancer elimination pillars should be simultaneous and cohesive, the scope of this document is to provide an overview of the technologies that are available for the screening, triage and treatment of cervical precancerous lesions and how they could be integrated into a cervical cancer secondary prevention strategy. It also includes brief descriptions of other non-technological methods and some considerations regarding product selection according to different models of service delivery and contexts (Figure 5).

Figure 5
Cervical cancer screening, triage and treatment-related products classified by technology type (blue boxes highlight the categories analyzed in more detail in this landscape review).



This landscape review is an update of a previous review conducted in 2019 . The current review has focused on:

- Further development of objective and transparent inclusion and exclusion criteria of different products, within each category, with emphasis on clinical validation and the existence of publicly available performance data (see section 2. Summary of Methods).
- Updating the categories of HPV tests, sampling devices and collection media, HPV oncogenic biomarkers, digital colposcopy, AI-based visual inspection and treatment devices.
- The provision of a "cost considerations" section, following product category analysis.
- The provision of more contextual and practical considerations as to how different technologies may be positioned in the cervical screening, triage and treatment pathway.

2.

Summary of methods

A set of inclusion criteria was defined for each technology category. Commercial availability (market authorization for any market) was a key inclusion criteria for all technologies included in the landscape; near-to-market technologies were also included in the horizon scan section.

The key stakeholders who informed the wide selection of manufacturers include Unitaid, the Bill and Melinda Gates Foundation (BMGF), The NHMRC Centre of Research Excellence in Cervical Cancer Control (C4) co-led by the Daffodil Centre, Clinton Health Access Initiative (CHAI), FIND, Global Health Labs and WHO.

Data were collected between October 2022 and November 2023 from multiple sources, including direct information from manufacturers, previous work conducted by Unitaid, peer-reviewed published literature, conference abstracts, institutional and corporate websites, product instructions for use (IFU) and through discussion with subject matter experts. Manufacturers were directly contacted via email at least twice. Some additional contacts for clarification and recent updates were made until May 2024. Only products with information submitted by the manufacturers were included for full description and analysis of their multiple features. Non-responders were excluded from this analysis.

A digital survey was conducted using questionnaires targeting different technical and use characteristics, jointly developed by key stakeholders along with expert advisors identified by WHO. In total, five questionnaires were developed, specific to: HPV nucleic acid amplification tests (NAATs) (hereafter, HPV tests), including DNA- and mRNA-based tests and other biomarkers; sample collection devices; collection/transportation media; AI- and digital-based visualization tools; and treatment devices for precancerous cervical lesions. Regarding treatment devices and enhanced visualization tools, a request for information (RFI) was opened for 4 weeks, starting on 22 December 2022 and included the digital survey with an intent to provide pertinent information about products that are either on the market (commercially available) or at a late stage of development.

As mentioned, this landscape only reflects an evaluation performed at a certain point in time and it is also important to recognize how dynamic the market and the validation processes are.

2.1 Inclusion criteria

HPV tests

Manufacturers were identified through direct consultation with key stakeholders, including via snowball sampling to identify further relevant stakeholders, and through the analysis of a 2020 comprehensive global inventory of commercially available HPV molecular tests [32]. Manufacturers of all clinically validated tests in this global inventory were added to the list and contacted for information about their products.

Commercially available tests (in any market) were included in this landscape if they were clinically validated. Clinical validation was assessed using the same approach used in the global inventory of commercially available HPV molecular tests [32] and therefore included assays that met at least one of the following criteria:

- U.S. FDA-approved – for U.S. regulatory approval, this stringent regulatory agency (SRA)[4] follows a rigorous evaluation process, requesting a high level of evidence to support the review of technologies. In general terms, large-scale clinical validation studies were required as part of the process for approval [33, 34]. This approval process is through the Premarket Approval (PMA) program and not through the Premarket notification 510 (k).

- Validated according to the International Guidelines for HPV DNA test requirements for primary cervical cancer screening in women 30 years and older (hereafter, Meijer criteria) [35] – these guidelines outline the minimum requirements for sensitivity, specificity and reproducibility (also available in this document on Table 2). Validated within the VALGENT study framework [36] – this framework enables comparison and validation of HPV genotyping assays using a relevant sample population with sufficient disease to confirm clinical performance using a validated comparator assay.

- WHO prequalified and indexed on the WHO list of prequalified in vitro diagnostics (IVDs) products.

4 Stringent Regulatory Authorities (SRAs) as defined in the WHO Technical Report Series 1003: Australia (TGA), Austria (AGES), Belgium (FAMPH), Bulgaria (BDA), Canada (Health Canada), Croatia (HALMED), Cyprus (MoH-PHS), Czech Republic (SUKL), Denmark (DKMA), Estonia (SAM), Finland (FIMEA), France (ANSM), Germany (BfARM), Greece (EOF), Hungary (OGYEI), Iceland (IMA), Ireland (HPRA), Italy (AIFA), Japan (PMDA), Latvia (ZVA), Liechtestein (Office of Health), Lithuania (VVKT), Luxembourg (MoH), Malta (Medicines Authority), Netherlands (MEB), Norway (NOMA), Poland (URPL), Portugal (INFARMED), Romania (ANMDMR), Slovakia (SUKLO), Slovenia (JAZMP), Spain (AEMPS), Sweden (SMPA), Switzerland (Swissmedic), United Kingdom of Great Britain and Northern Ireland (MHRA), United States of America (US-FDA), European Medicines Regulatory Network

Table 2
Clinical performance criteria for HPV tests, according to Meijer criteria

Performance parameter	Sample specification	Performance
Sensitivity	At least 60 cervical specimens from a population-based screening cohort of women greater than 30 years with histologically confirmed CIN2 or greater	At least 90% of the sensitivity of the standard comparator for detection of CIN2 or greater.
Specificity	At least 800 cervical specimens from a population-based screening cohort of women ≥ 30 years with histologic confirmation of no CIN2 or greater present	At least 98% of the specificity of the standard comparator for detection of CIN2. [35, 37]
Inter-laboratory agreement and intra-laboratory reproducibility	At least 500 samples, 30% of which tested positive in a reference laboratory using a clinically validated assay. Same intra-laboratory reproducibility performance criteria should be reached after testing the same set of samples several weeks later	Inter- and intra-laboratory agreement of results of at least 87%.

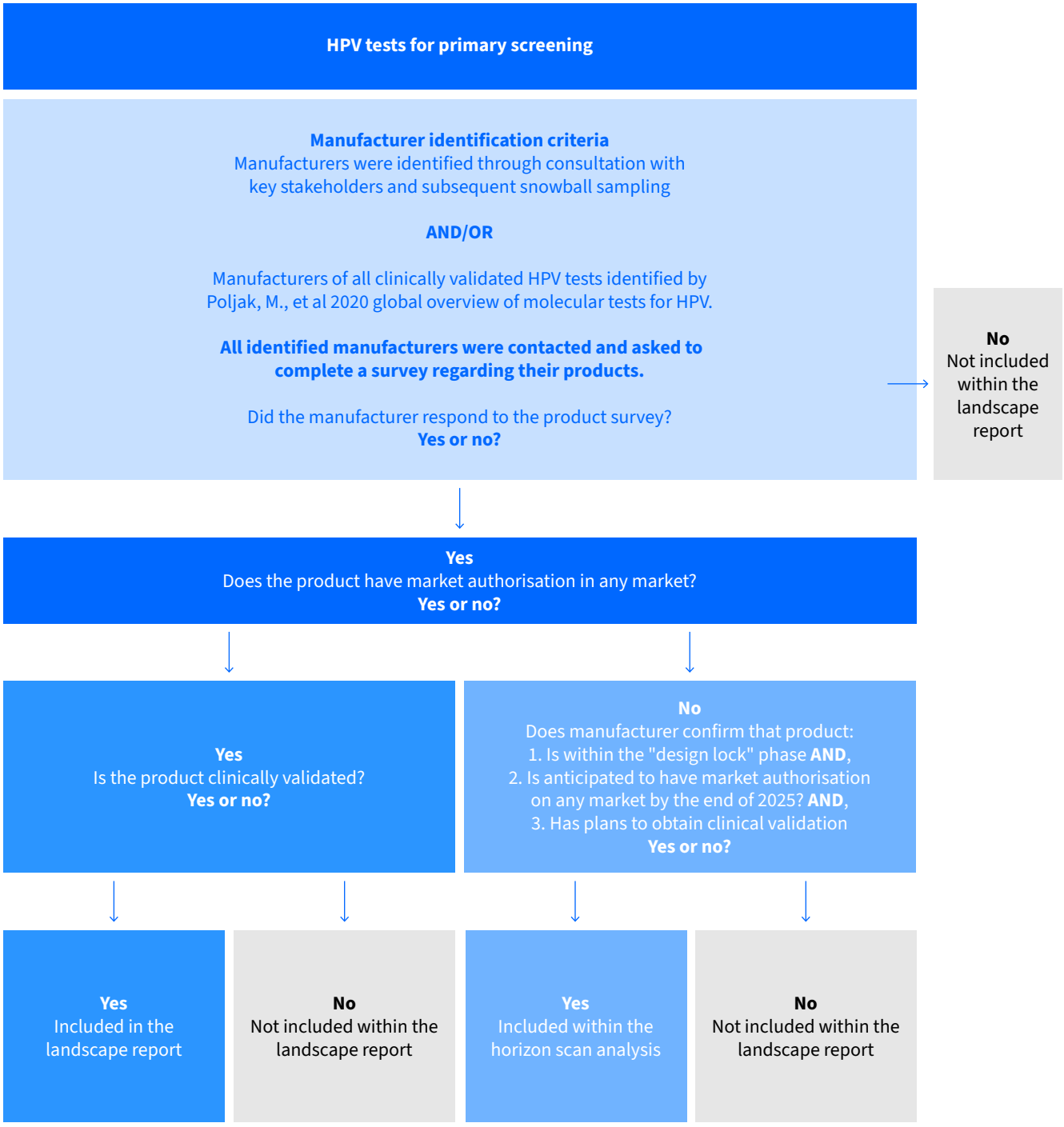
The horizon scan included tests that manufacturers had confirmed were not commercially available yet, but were:

- Design-locked (defined as, at final stage of development, where design has been optimized to closely meet the desired performance specifications, ensuring that all outputs are adequately transferred to production [38]),
- Targeting market authorization on any market by the end of 2025, and
- Planning clinical validation against CIN2+ outcomes.

This horizon scan section was created to capture innovative products that could potentially respond in the future to some unmet needs of the market. The inclusion criteria were developed to minimize the inclusion of products that may not reach the market; however, it is important to note that the products included in the horizon analysis may never become commercially available and/or satisfy clinical validation criteria. At the same time, there are products on the market/commercially available that have not been clinically validated (according to the above-outlined criteria); these products have not been included in this version of the landscape.

Figure 6 summarizes the inclusion/exclusion criteria algorithm for included primary HPV tests.

Figure 6
Inclusion and exclusion criteria of HPV tests for primary screening in the landscape and horizon scan analysis



Sampling devices and media

Manufacturers were identified through consultation with key stakeholders. All swabs and brushes (sampling device types compatible with the WHO 2021 guidelines) that have market authorization in any market, were included in this landscape. The horizon scan included other types of sampling devices that are not currently recommended by the guidelines and that may have implementation benefits in the future, but still with limited performance data available.

Triage technologies

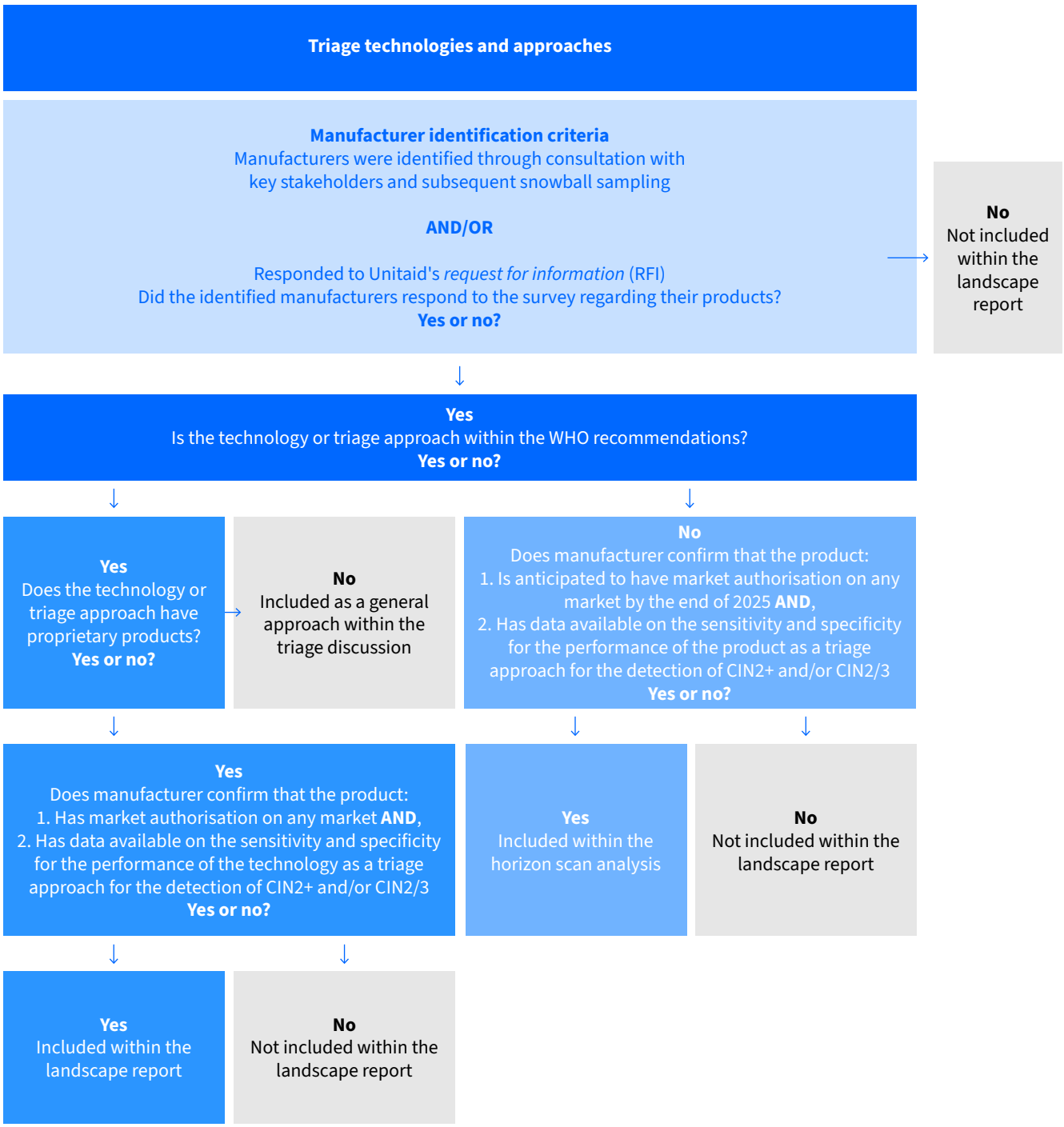
Manufacturers were identified through direct consultation with key stakeholders and through the previously described RFI.

Triage technologies and approaches that are recommended in WHO 2021 guidelines were included in the landscape; those involving proprietary products should be available in market (any market) and have data available on sensitivity and specificity for the performance of the product as a triage method, for the detection of CIN2+ and/or CIN2/3. This clinical performance evaluation should have been performed on at least 100 cervical specimens from a population-based screening cohort of women, and the data should be publicly available, either as part of the product labelling or published in a peer-reviewed journal. If the triage approach does not involve a proprietary product, such as VIA, a general description was included in the triage discussion section.

Triage technologies and approaches that are still under evaluation and thus are not currently recommended by WHO, were considered for the horizon analysis. To be included in this section, manufacturers had to confirm that the product is planned to be on any market by the end of 2025 and will have available performance evaluation data as described above.

Figure 7 represents the inclusion/exclusion criteria algorithm for triage technologies and approaches, excluding HPV partial genotyping. For HPV partial genotyping, only tests that are also suitable for primary screening and are clinically validated were considered. The use of partial genotyping as a triage method assumes that the partial genotyping outputs harness the capacity of a relevant HPV test for primary screening, and that partial genotyping is used in accordance with the relevant WHO algorithm for screen-triage-and-treat.

Figure 7
Inclusion and exclusion criteria for triage technologies and approaches in the landscape and horizon scan analysis (excludes partial genotyping, as only HPV tests suitable for primary screening were considered for partial genotyping)



Precancer treatment devices

Manufacturers were identified through direct consultation with key stakeholders and through the previously described RFI, targeting cervical precancerous lesions treatment devices.

All precancer treatment devices that have market authorization in any market and performance/treatment efficacy and safety data available were considered for this landscape. The horizon scan included innovative pipeline products, planned to be on any market by the end of 2025, with performance data available.

2.2 Data presentation and analysis

The main features of each – category of products are displayed in 8 different technology tables along this landscape document, accompanied by analysis summaries and specific cost considerations:

Technology table 1	Clinically validated HPV tests and platforms commercially available for primary screening (includes tests that can be used for triage with partial genotyping)
Technology table 2	Horizon scan for pipeline HPV tests in late stage of development
Technology table 3	Protein-based biomarkers and DNA methylation tests for triage Horizon scan - in late-stage of development and/or ot recommended in the WHO 2021 guidelines
Technology table 4	Sampling devices for HPV testing (includes horizon scan products)
Technology table 5	Dual-stain cytology for detection of p16 and Ki-67
Technology table 6	Enhanced visual assessment tools, including digital imaging and AI-based solutions (Horizon scan – not recommended in the WHO 2021 guidelines)
Technology table 7	Digital colposcopy - imaging specific features
Technology table 8	Devices for treatment of precancerous lesions (includes horizon scan products)

To showcase real-world implementation within different contexts and using alternative cervical cancer screening approaches and technologies, four case studies are presented within this report:

Case study 1	Screen-and-treat using point-of-care (POC) HPV testing in Papua New Guinea
Case study 2	Health service integration of HPV screening in Nigeria
Case study 3	Project ROSE, pilot study of self-collection approach with digital registry support
Case study 4	Multicountry Unitaid-supported project using thermal ablation devices

3.

Molecular testing

RECOMMENDED FOR PRIMARY SCREENING

3.1 HPV testing

3.1.1 Recommendations on transitioning to HPV tests for primary screening

HPV tests are being progressively incorporated into screening programs worldwide, with many LMICs considering scaling-up HPV testing by 2030. The WHO regional offices of the South-East Asia Region (SEARO), Western Pacific Region (WPRO) and the Eastern Mediterranean Region (EMRO) have developed and published tailored strategic frameworks at the request of and in consultation with their Member States, to give guidance and support to the implementation of WHO's cervical cancer elimination strategy in their particular settings [39, 40]. Recent implementation studies have proven that HPV DNA tests are acceptable and feasible for use in LMICs, if sufficient resources and supportive infrastructure linking patients to follow-up care exists [41-43].

HPV tests are recommended to be implemented via either the *"screen and treat approach"* or the **"***screen, triage and treat approach"* for the general population. In a *"screen and treat approach"* there is no requirement for a second test prior to ablative treatment. However, women living with HIV should be screened with algorithms that include a triage step [2]. The simplicity of these algorithms helps to support implementation, with improved uptake and reduced loss to follow-up. Seven different algorithms have been described and evaluated as part of the development of the WHO 2021 guidelines.

Programs should mirror best practices for other laboratory programs and encompass aspects of health care worker training, laboratory processing, quality assurance, supportive systems and overall program implementation. The WHO 2021 guidelines critically note that while implementing cost-effective screening technologies is crucial to elimination, the need for screening program coherence and the guarantee of continuity of care is equally important. This relies on efficient follow-up of participants and timely and appropriate treatment of HPV-positive women [38], supported by screening registries and other health information systems enabling participant data exchange across all levels of health care providers.

3.1.2 HPV test categories

Cervical HPV testing aims to detect the presence of HPV infection through amplification of nucleic material [44, 45] (viral genomic DNA [HPV DNA tests] or viral messenger RNA [HPV mRNA tests]).

DNA-based HPV tests have been recommended by WHO as the primary screening test for both the general population of women and women living with HIV. However, mRNA-based HPV tests are only recommended as an alternative for the general population of women; due to an absence of evidence, which has not allowed recommendations to be made for the use of HPV mRNA tests

for women living with HIV or in the context of self-sampling. mRNA HPV tests are also only recommended in the context of 5-yearly screening, as at the time of guidelines review, strong evidence around the performance of these tests beyond 5 years is not yet available (there has been some subsequently emergent data, but this has not been formally reassessed in terms of the living guidelines framework to date). Currently, therefore, choosing an mRNA-based HPV test requires the programmatic capacity to screen every 5 years, and HPV DNA testing should be used for women living with HIV and if self-collected samples are to be used (Figure 8).

Figure 8

Comparison of HPV NAATs: HPV DNA and HPV mRNA. Source: Human papillomavirus (HPV) nucleic acid amplification tests (NAATs) to screen for cervical pre-cancer lesions and prevent cervical cancer – WHO policy brief

Recommended use of HPV DNA mRNA NAATs	HPV distinct tests
HPV DNA NAATs	**HPV mRNA NAATs**
Recommended* as the preferred primary screening test in both "screen-and-treat" and "screen, triage and treat" strategies to prevent cervical cancer in the general population, starting at age 30	Suggested* as an alternative primary screening test in both "screen-and-treat" and "screen, triage and treat" strategies to prevent cervical cancer in the general population, starting at age 30
Recommended* as the preferred primary screening test and suggested* for use within a "screen, triage and treat" strategy to prevent cervical cancer in women living with HIV, starting at age 25	No recommendation for use in women living with HIV because no applicable evidence was identified
5- to 10-year screening intervals suggested* in the general population, and 3–5 years in women living with HIV	5-year screening intervals suggested* in the general population
Samples taken by health-care provider OR self-collected	Samples taken by health-care provider ONLY

* **"Recommended"** = strong recommendation; **"suggested"** = conditional recommendation.

3.1.3 HPV DNA-based molecular tests

HPV DNA tests detect high-risk HPV DNA in vaginal and/or cervical samples. HPV DNA tests can detect high-risk HPV genotypes in a single channel or can detect HPV types separately (such as 16, 18 +/- 45), generally referred to as "partial genotyping" which can be used for triaging of women with HPV-positive test. As HPV 16 and HPV 18 together are responsible for approximately 70% of all cervical cancers globally, some HPV tests target exclusively these two most common high-risk oncogenic genotypes. Among commercially available tests, the results are generally reported as "detected" or "not detected", although some tests can report HPV genotypes individually or pooled in type-groups with various possible combinations of types [45]. The assays that separately identify more than HPV 16 and 18 are referred to as having "extended genotyping" and, at the time of writing, the extended genotyping capacity of such tests are not specifically recommended for use in triaging by WHO.

Self-collected HPV DNA tests do not require a pelvic examination with a speculum, as vaginal samples may be collected by the woman either in her home or in the clinic under the guidance of a health care provider, approaching the same level of accuracy and sensitivity as via collection by the health care provider [46].

Sensitivity and specificity of HPV DNA tests

Most significantly, HPV DNA testing has consistently very high sensitivity for the detection of CIN2+, reaching sensitivity levels near 95-100% [47]. This means a negative HPV DNA test identifies women at very low risk of development of precancerous or cancerous lesions (CIN3+) within five years (a very high negative predictive value) [2, 3], and therefore, screening intervals can be longer than for VIA or cytology. Additionally, VIA relies heavily on the skills and experience of the operator, leading to high subjectivity and a large variation in accuracy (sensitivity and specificity) [48]. Consequently, HPV DNA testing at a population level is a more cost-effective tool than VIA or cytology, despite the costs for individual tests being higher [49]. This is because of the better sensitivity of the test, allowing much longer screening intervals, and the higher sensitivity for detecting CIN2+ and CIN3+ at any one screen.

It is important to note that a positive HPV test does not indicate precancer; it only confirms that there is an HPV infection with a potentially oncogenic type. As HPV infection and precancerous lesions often spontaneously resolve, HPV DNA testing if implemented without triage has a lower specificity for cancer and precancerous lesions, often lower than the specificity for that of cytology [50]. If not carefully managed this lower CIN2+ specificity of HPV tests and lower PPV for precancerous lesions may lead to overtreatment, particularly in women living with HIV [22, 23]. Appropriate selection of the age range of screening is one way in which this issue is managed. In the WHO 2021 guidelines, potential harms were balanced with the benefits and programmatic costs in the evaluation. For the general population of women, the HPV 'screen-and-treat' approach is appropriate in some contexts, but the 'screen-triage-and-treat' can be chosen if resourcing is available to further reduce harms. For women living with HIV, it is recommended that triaging is performed, as in this population, HPV DNA tests have lower specificity for precancerous disease [22]. Currently, triage approaches recommended by WHO include partial genotyping, colposcopy, VIA and cytology.

3.1.4 HPV mRNA-based molecular tests

Since HPV mRNA tests detect E6/E7 oncoproteins, a more downstream component in the development of precancerous changes, HPV E6/E7 mRNA detection theoretically allows for higher specificity than HPV DNA detection [18].

Sensitivity and specificity of HPV mRNA tests

Some evidence exists for the safe and effective use of HPV mRNA, showing similarly high rates of performance relative to HPV DNA testing at baseline. Compared to HPV DNA testing, HPV mRNA sensitivity is similarly sensitive (relative sensitivity 0.98) and slightly higher specificity (1.03 relative specificity) for detection of CIN2+ [32]. However, data suggest a performance degradation with self-collected samples and there is a relative lack of long-term data on mRNA efficacy, particularly for women living with HIV, and in LMIC. The more recent emergence of further longitudinal data is important and will continue to be considered in the context of living WHO guidelines [51].

HPV mRNA tests have similar costs, training and equipment requirements to DNA-based HPV testing. Based on data available at the time of this landscape development, overall costs over a woman's lifetime may be 6-10% lower with HPV mRNA testing than with HPV DNA testing, however since longer screening intervals are possible with HPV DNA testing than with mRNA testing (5 to 10 years *versus* five years interval, among the general population), HPV DNA testing may result in the use of fewer resources overall [18].

A final consideration is the acceptability of mRNA testing, as currently only cervical sample collection by a health care provider is recommended rather than self-collection [18].

3.1.5 HPV testing platforms

The testing platforms vary in size, infrastructure requirements, portability, required operator qualifications, throughput, and other operational characteristics (as shown in Figure 9). The selection of a testing platform should be based on a service delivery model that is affordable, operationally feasible and sustainable for each country.

Figure 9
Comparison of different in vitro diagnostic (IVD) HPV tests

Testing method	Manual	Automated	Point-of-care or near-patient testing
Manual steps	Maximum	Limited	Limited
Operator qualifications	Experienced in laboratory procedures	Trained for specific automation	No laboratory experience needed; focused device training
Throughput	Small to moderate batch testing	High volume batch testing, but random access available	Single specimen, but can combine multiple modules to increase volume
Infrastructure requirements	Vast majority of methods require reagent-grade water, continuous, reliable power supply Requires appropriate chemical and biohazard waste management	Reagent-grade water, continuous, reliable power supply, significant laboratory footprint Requires appropriate chemical and biohazard waste management	Continuous, reliable power supply Requires appropriate chemical and biohazard waste management
Advantages	Lower initial investment	High throughput, limited operator involvement	Facilitates "screen and treat" programmes, no laboratory experience needed to operate
Limitations	Labour-intensive	High initial investment; large footprint	Low throughput (though moderately scalable to increase capacity)

Source: Adapted from WHO, 2020.

True POC HPV testing technologies process tests directly at the sample-collection site with minimal infrastructure or training requirements, while near-POC technologies require basic lab infrastructure, trained technicians, and consistent water and electricity sources to operate. Both tests typically include shorter test run times, which may enable the return of results and any follow-up care within a single visit. Laboratory-based platforms are capable of higher throughput and are often associated with lower costs per test than POC; yet they also require more advanced laboratory infrastructure and more operator qualifications and training. Thus, they may be particularly suitable for urban/semi-urban areas, with adequate sample transport networks and/or centralized testing facilities where the population is more concentrated. For countries with shortages of skilled labor or unable to provide more specialized training, automated systems that simplify the testing process and reduce potential human error may be appropriate.

WHO is currently updating target product profiles (TPP) for tests to detect HPV, including a lab-based TPP and the development of a new TPP related to POC tests, to reflect the needs highlighted in WHO 2021 guidelines.

Countries with existing testing platforms can consider the integration of HPV testing to reduce initial set-up and procurement costs. Integrating HPV testing into other testing platforms, such as those for tuberculosis diagnosis, HIV early infant diagnosis or HIV viral load or those introduced for COVID-19 testing, is feasible and should be considered, especially as many systems have excess capacity. However, prioritization of disease-type tests may be challenging and constitute a barrier to timely HPV results.

While up-and-coming POC testing modalities seek to increase the feasibility and availability of HPV testing in LMICs, it is emphasized that countries should select the testing method that is most affordable, appropriate and effective for their own setting [32, 52]. Where centralized testing platforms already exist or it is not possible to guarantee a single-visit approach, a centralized testing approach may be more efficient due to economies of scale while taking into consideration cost barriers and risk of loss-to-follow-up [41]. However, different testing platforms may co-exist within the same country, as there might be different contexts and communities with particular needs. For example, in an urban center, laboratory-based testing centralized at the hospital may be the most appropriate, while in rural areas with more constrained access to testing services, POC/near-POC testing, offered at local health facilities, may be the preferred option. Laboratory network optimization should be done under the leadership of and in consultation with the national laboratory directorate, so developing a national laboratory network plan will be essential to construct a concerted national testing strategy that will support the screening program.

Screen-and-treat using point-of-care HPV testing in Papua New Guinea

Papua New Guinea (PNG) has the highest cervical cancer incidence and mortality rates in the Asia-Pacific region. Compared with Australia, the age-standardized incidence of cervical cancer in PNG is five times higher (29.4 cases per 100,000 people vs. 6 cases per 100,000 people), and the mortality rate is 12 times higher (19.8 cases per 100,000 people vs. 1.7 cases per 100,000 people) [53].

Earlier screening initiatives for women in PNG, established by an Australian-supported charity (the *MeriPath* program) in 1999, were only able to achieve modest coverage, with around 45,000 women screened over ten years (2001-2011), representing less than 4% of the target age-eligible population [54]. Even when women were screened, more than half of cases positive for the high-grade disease were lost to follow-up, as specimens had to be sent to Australia, and there was a significant delay between testing and recall [55]. These programs were revaluated by a *Ministerial Task Force on Cervical Cancer* in 2009, which recommended the evaluation of a 'screen-and-treat' approach endorsed by WHO for LMICs, based on VIA followed by ablative cervical cryotherapy [56]. The success of this program was limited due to VIA's poor performance as a primary screening tool, even when used in combination with HPV DNA testing, reflecting broader findings from LMICs. VIA was therefore considered inappropriate for primary screening and clinical triage of HPV-positive women in this setting [55, 56].

Since these discoveries, two major interventional studies (a 2016 field evaluation, and HPV STAT, a prospective single-arm intervention trial from 2018 to 2020) have evaluated a new point-of-care HPV self-collect, testing and treatment approach among more than 5,000 women in the Eastern Highlands, Madang and Western Highlands provinces of PNG [57, 58]. These studies integrated HPV DNA testing on the GeneXpert platforms (Cepheid, USA) using self-collected vaginal specimens followed by same-day thermal ablation or gynecological referral for HPV-positive women. HPV screen-and-treat had excellent clinical performance for same-day detection and treatment of cervical precancer; could be safely delivered at scale by trained nursing staff in routine primary health facilities; and was highly cost-effective and efficient compared to VIA-based primary screening [55, 58, 59]. Self-sampling processes were also highly acceptable among women, their families, and health workers facilitating greater participation and comfort during screening.

A subsequent modelling study found that this model was both effective and cost-effective, and if scaled up rapidly, could prevent over 20,000 deaths over the next 50 years [59]. Conversely, VIA screening was not effective or cost-effective [59]. These findings support the introduction and scale-up of same-day HPV screen-and-treat, being effective, safe and acceptable when used in clinical settings, and have now been adopted for implementation nationally in PNG and Vanuatu, supported by a western Pacific regional partnership for the elimination of cervical cancer.

Ongoing endorsement from governmental departments and philanthropic and industrial partnership is essential to ensure the necessary expansion and strengthening of cervical cancer prevention programs.

Funding: VIA Study/Sik blo Mama - Australian Aid Program, Department of Foreign Affairs and Trade, Government of Australia; HPV POC Study – PNGIMR ICRAS Award, Government of PNG, Australian Aid Program, Department of Foreign Affairs and Trade, Government of Australia; HPV-STAT / C4 CRE - National Health and Medical Research Council, Australia; ECCWP – Minderoo Foundation, Cepheid, Copan, Asia Development Bank, Frazer Family Foundation, Governments of PNG and Vanuatu

3.1.6 Reagent and consumables for HPV testing

A critical step in a country's transition from cytology or VIA based cervical screening to HPV based screening is the selection of an appropriate and quality assured HPV test and the required reagents and consumables [32, 60, 61]. HPV tests are diverse in terms of sample required, collection device, transport media, nucleic acid extraction methods required, assay format and instrument capacity. Novel HPV assays are also in various stages of development and regulatory approval, leading to a complex picture of relative advantages and disadvantages when comparing available assays. Poljak, M et al. (2024) have outlined the seven main groups of commercially available HPV molecular tests, and their performance and regulatory approvals were summarized at the time of publication (Table 3) [61].

Table 3

Seven main groups of commercially available HPV molecular tests on the global market in December 2023 (reproduced from Poljak et al., 2024)

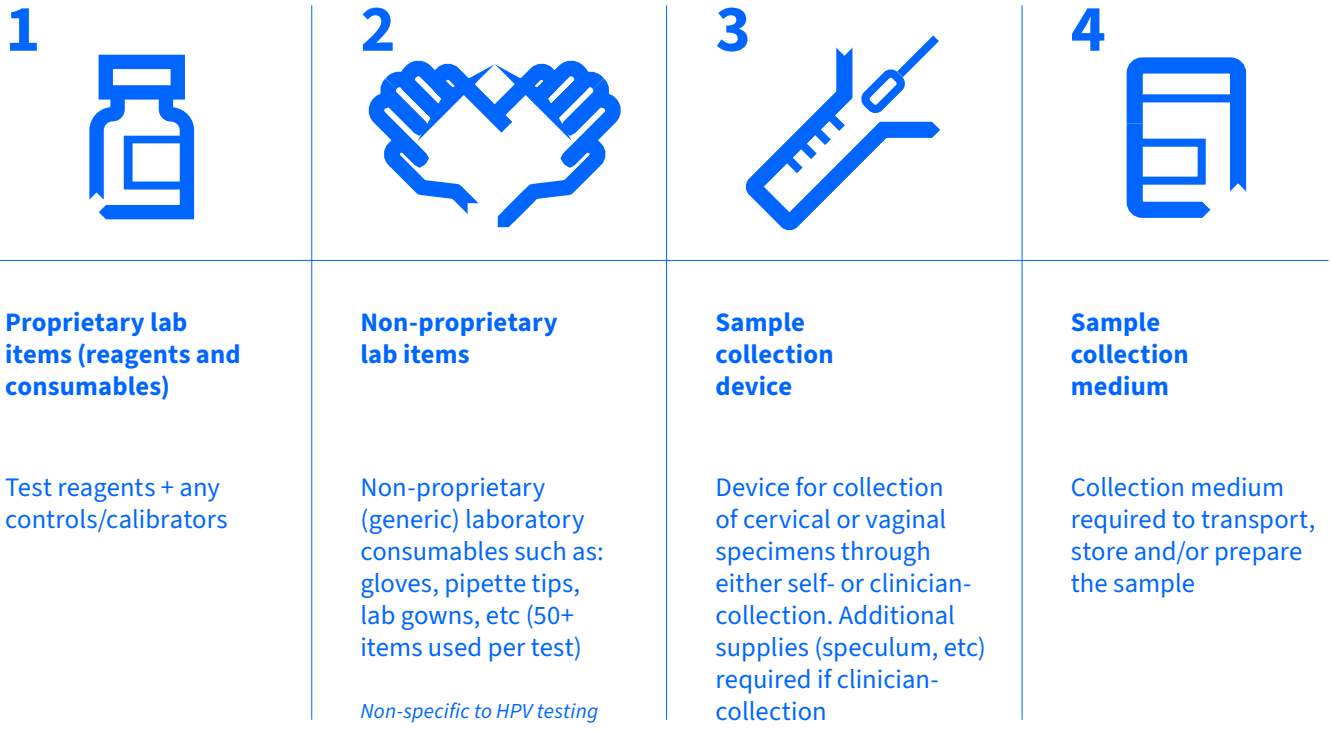
Commercially available HPV molecular tests present on the global market in December 2023. For the purpose of this inventory distinct HPV tests and their variants are divided into seven main groups and several subgroups based on tests' technology used and targeted HPV genotypes. A full list of all individual HPV tests and their manufacturers is provided in Supplementary Tables S1–S6 of the 2023 global inventory of commercial molecular tests for human papillomaviruses (HPV). Poljak et al., 2024.

HPV test group	HPV distinct tests	HPV tests variants
hr-HPV DNA screening tests without genotyping	**29**	**9**
Tests targeting 12 IARC-2009 hr-HPV genotypes plus HPV66 and/or HPV68	16	1
Tests targeting 12 IARC-2009 hr-HPV genotypes only	4	2
Tests targeting 12 IARC-2009 hr-HPV genotypes and additional alpha-HPV genotypes	9	4
Tests targeting a subset of 12 IARC-2009 hr-HPV genotypes	0	2
hr-HPV DNA screening tests with concurrent partial (HPV16/18/45), concurrent extended or reflex partial genotyping for the main hr-HPV genotypes	**64**	**10**
hr-HPV DNA screening tests with concurrent partial (HPV16/18/45) genotyping for the main hr-HPV genotypes	55	10
hr-HPV DNA screening tests with concurrent extended genotyping for the main hr-HPV genotypes	5	0
hr-HPV DNA screening tests with reflex partial genotyping for the main hr-HPV genotypes	4	0
HPV DNA full genotyping tests	**84**	**29**
Strip, filter or microtiter-well hybridisation-based full genotyping tests	21	4
Gel electrophoresis–based full genotyping tests	1	0
Real time PCR-based full genotyping tests	38	21
Medium- or low-density microarray-based full genotyping tests	14	4
Microsphere bead–based full genotyping tests	5	0
Capillary electrophoresis–based full genotyping tests	2	0
Full genotyping tests based on PCR combined with matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry	1	0
Full genotyping tests based on PCR combined with sequencing	2	0
HPV DNA genotype- or group-specific genotyping tests	**42**	**100**
Strip, filter or microtiter-well hybridisation-based genotype- or group-specific genotyping tests	2	1
Gel electrophoresis–based genotype- or group-specific genotyping tests	2	22
Real time PCR-based genotype- or group-specific genotyping tests	36	75
Loop-mediated isothermal amplification and electrochemical DNA chip	2	2
hr-HPV E6/E7 mRNA tests	**9**	**3**
in situ hybridisation DNA- and mRNA-based HPV tests	**35**	**360**
HPV DNA tests targeting multiple non-Alpha HPV genotypes	**1**	**0**
Total number of HPV tests	**264**	**511**

Selection of an HPV assay requires consideration of a suitable HPV test platform together with the required reagents and consumables. These include proprietary laboratory items, typically included as HPV test reagents and consumables from the test supplier, non-proprietary laboratory items and consumables, sample collection devices and sample collection media (Figure 10). Depending on the assay and platform, there might also be a need for some auxiliary equipment, like centrifuge, vortex, heating block, computer. In some cases, transport media may not be required - as in the case of self-collection where dry transport is available – and, for some assays, the medium is included in a bundle with the reagent.

For this landscape report, we have focused on proprietary HPV test reagents and consumables, sample collection devices and sample collection media.

Figure 10
Reagents and consumables for HPV testing



Source: Adapted from CHAI, 2022

3.1.7 Additional considerations when selecting HPV test technologies

Many HPV testing technologies, as well as other technologies needed for the cervical screening pathway, exist and are entering the market. However, besides choosing clinically validated methods and technologies, it is also important to have a context-appropriate testing network, matching the needs of a country's identified use-case [60].

The WHO 2021 guidelines closely reviewed evidence on the benefits and harms of several screening techniques applied within simple algorithms, to improve strategies for screening and treatment to prevent cervical cancer worldwide. Additional guidance to support program managers towards effective implementation, scale-up and sustainability of HPV-based screening and treatment strategies is being completed, summarizing the current knowledge on multilevel (target population, providers and health systems) approaches and interventions used to implement WHO recommendations. A step-by-step WHO guide for introducing and scaling up HPV testing is also available to provide support following the decision to introduce HPV testing, that includes a methodology for selection of testing products [2, 60].

One of the models of care recommended in the WHO 2021 guidelines when using a 'screen-and-treat' approach is the single-visit model, meaning if the patient is eligible for ablative treatment, this should ideally be done immediately at the same visit as the screening test, to help to reduce loss to follow-up, especially in more remote areas. However, for many different reasons, this is not always feasible, and a second visit is needed (the multiple-visit approach). A recent study assessing HPV testing implementation across 45 primary and secondary health clinics in Malawi, Nigeria, Senegal, Uganda and Zimbabwe showed HPV testing was feasible, although attrition was seen at several key points in the cascade of care, and only 25% of women received their test result the same day, linking to triage and appropriate treatment [41]. Also, this single-visit approach may be of lesser value in some specific contexts, like when women have to attend a health care service regularly (e.g., women living with HIV) or in urban areas.

WHO also supports models using self-sampling, as this collection method is seen as highly acceptable in terms of privacy and comfort (including decreased embarrassment, pain and anxiety), convenience, user-friendliness, ease, time and effort saved, cost-effectiveness, safety, and generally associated with increased uptake of cervical cancer screening services [37].

Case study 2

Health service integration of HPV screening in Nigeria

With an incidence of 18.4 per 100,000 and mortality of 13.2 per 100,000, cervical cancer remains a leading burden of disease amongst women in Nigeria [62]. As of 2019, screening coverage rates in Nigeria hovered around 13% for both Women Living with HIV (WLHIV) and all women 30-49 years of age, with Pap smear and VIA in use as the predominant screening modality.

In collaboration with CHAI and supported by Unitaid, a pilot was conducted by the Nigeria FMoH to demonstrate a pathway for the introduction and scale-up of HPV DNA testing in the country. The approach depended heavily on integrating services across the care cascade from demand generation to screening and through to systems for follow-up and referral.

Activities for demand generation leveraged Social and Behavioral Change Committees, maternal/child health campaigns, community- and faith-based organizations, as well as community agents such as traditional birth assistants (TBAs) and Patent and Proprietary Medicines Vendors (PPMVs) to promote cervical cancer messaging and to conduct community outreaches to reach women with screening and treatment services. Collaboration with PEPFAR Implementation Partners, advocacy groups such as Network of People Living with HIV and AIDS in Nigeria (NEPWHAN), and State AIDS and STI control programs further extended the program's reach, particularly among WLHIV. To expand access, screening was integrated into reproductive health services, and various departments, including Family Planning, Labor & Delivery, Antenatal Care and ART clinics, were tasked with offering screening services.

At the laboratory level, in collaboration with PEPFAR, HPV testing was introduced onto underutilized PCR platforms in country. Within Nigeria, approximately 30 centralized and 400 decentralized devices exist, capable of providing HPV testing. By introducing HPV on just 16 (38%) of the existing devices, HPV services were able to be offered at 207 screening sites – 6% offering decentralized testing using GeneXpert, while the vast majority (94%) offered testing via centralized platforms (Hologic Panther or Roche cobas). Furthermore, in Niger State, the State was able to leverage the National Integrated Sample Referral Network (NiSRN) to transport HPV samples to and from the testing lab, and this sustainable model is being expanded to other states.

To facilitate patient tracking across the entire care cascade, focal nurses at facilities were trained as patient navigators to track sample transport to labs, communicate results to patients via phone calls, and request women with HPV+ results to return to the facility for subsequent care. Through the introduction of thermal ablation devices in December 2020, treatment for most precancerous lesions was able to be provided right at the primary health care level.

Through 2023, the program was able to screen over 53,000 women (36% WLHIV) and link ~98% of treatment-eligible women with follow-up care. Combined with improvements to VIA screening programming, coverage was increased to 39% amongst WLHIV and 16% amongst all women 30-49 years of age within program states.

Building on these efforts, the national strategy for cervical cancer was detailed in the National Strategic Plan for Prevention and Control of Cancer of the Cervix in Nigeria (2023-2027). This updated national strategic plan strongly recommends HPV DNA testing as a primary screening strategy, with a target of screening 50% of eligible women at least twice in their lifetime by 2027. However, where this is unavailable, use of VIA/VILI, cytology and other screening methods is encouraged. Continued investment in priority areas is critical to maintain momentum for screening and treatment programs while long-term sustainable funding is identified and institutionalized.

3.1.8 HPV testing technologies landscape

A 2023 scoping review of the global market for available molecular HPV tests indicated a rapid and sometimes unregulated growth of the HPV testing market [61]. Approximately 264 distinct HPV tests and 511 test variants were found to be available on the global market, representing a 37% increase compared with a previous assessment in 2015. Of these tests, 50% were shown to be without a single supporting peer-reviewed publication, and 79% lacked published analytical and/or clinical evaluation.

To account for the breadth of non-quality assured HPV products on the market, this landscape analysis will focus on clinically validated commercially available HPV tests (technology table 1) and a horizon scan focuses on some late-stage development pipeline products (technology table 2) according to the inclusion criteria described within the Methods section.

Technology table 1

Clinically validated HPV tests and platforms commercially available for primary screening (includes tests that can be used for triage with partial genotyping)

HPV tests for primary screening												
Manufacturer	**Assay name**	**Platform**	**Clinical validation** (1)			**HPV 16/18 Genotyping** (2) and additional information	**Self-sampling - vaginal sample** (listed on IFU) (3)	**Test run time (90 minutes or lower)** (4)	**Capacity** (high/med/low throughput) (5)	**Test processing** (batched / random access) (6)	**Level of automation** (full / partial / manual) (7)	**Storage requirements**
			FDA approval	Meijer's Guidelines and/or VALGENT Initiative	WHO Prequalified (year)							
HPV DNA tests												
DNA target amplification (isothermal or real-time PCR)												
Abbott	Alinity m High Risk (HR) HPV	Alinity m	✓	✓	✗	✓ HPV 16, 18 individually; other hrHPV pooled (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	✗	✗ (< 115 minutes)	High	Random Access	Full Automation	Amplification kit: -25°C to -15°C Control kit: ≤ -10°C
Abbott	RealTime High Risk (HR) HPV	m2000 sp/rt	✗	✓	✓ (2019)	✓ HPV 16, 18, 45 individually; 2 other hrHPV groups: (31, 33, 52, 58); and (35, 39, 51, 56, 59, 66, 68)	✗	✗ (5.5 hours)	Med	Batched	Partial Automation	Amplification kit: -25°C to -15°C Control kit: ≤ -10°C Shelf-life: 18 months
BD	BD Onclarity HPV Assay	BD Viper™ LT / BD COR™ System	✓	✓	✗	✓ HPV 16, 18, 31, 45, 51, 52 individually; 3 other hrHPV groups: (33,58); (56,59,66); and (35,39,68)	✗	✗ (4 hours)	Low (Viper LT) Med (COR)	Batched	Full Automation	Room Temperature (2-33◦C)
Cepheid	Xpert® HPV	GeneXpert (I, II, IV, XVI, Infinity-48, Infinity-80)	✗	✓	✓ (2017)	✓ HPV 16, 18, 45 individually; other hrHPV pooled: (31, 33, 35, 39, 51, 52, 56, 58, 59, 66, 68)	✗	✓ (60 minutes)	Range of Low (IV) to High (Infinity-80)	Random Access	Full Automation	Room Temperature (2-28◦C) Shelf-life: 18 months
QIAGEN	*NeuMoDx™ HPV Test Strip* – discontinued in 2024, *phasing out to be completed in 2025*	*NeuMoDx-96, NeuMoDx-288*	✗	✓	✗	✓ *HPV 16, 18 individually; other hrHPV pooled: (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 67, 68)*	✓	✓ *(60 minutes)*	*Low - Med*	*Random Access*	*Full Automation*	*15 to 23 °C*
QIAGEN / Self-screen B.V.	QIAscreen HPV PCR Test	Rotor-Gene Q MDx system (Need to do DNA extraction before PCR)	✓	✓	✗	✓ HPV 16,18 individually; other hrHPV pooled: (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 67, 68)	✓	✗ (3 hours)	Low	Random Access	Manual	–30°C to –15°C Shelf-life: 18 months
	HPV Risk Assay	Mic qPCR cycler	✗	✓	✗	✓ HPV 16, 18 individually; other hrHPV pooled: (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 67, 68)	✓	✗ (5 hours)	Low-Med	Batched	Partial Automation	-20°C in the dark Shelf-life: 18 months
Roche	cobas® HPV test (5800/ 6800/ 8800)	cobas® 5800/ 6800/ 8800 systems	✓	✗	✓ (2023)	✓ HPV 16, 18 individually; other hrHPV pooled: (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	✓	✗ (< 3.5 hours)	Med (5800) High (6800/8800)	5800 - up to 3 tests without batching 6800/8800-Random Access	Full Automation	Refrigerator 2–8°C Shelf-life: 24 months

HPV tests for primary screening												
Manufacturer	**Assay name**	**Platform**	**Clinical validation** (1)			**HPV 16/18 Genotyping** (2) and additional information	**Self-sampling - vaginal sample** (listed on IFU) (3)	**Test run time (90 minutes or lower)** (4)	**Capacity** (high/med/low throughput) (5)	**Test processing** (batched / random access) (6)	**Level of automation** (full / partial / manual) (7)	**Storage requirements**
			FDA approval	Meijer's Guidelines and/or VALGENT Initiative	WHO Prequalified (year)							
Roche	cobas® HPV test (4800)	cobas® 4800 system	✓	✓	✗	✓ HPV 16, 18 individually; other hrHPV pooled: (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	✓	✗ (5 hours)	Med	Batched	Partial Automation	Refrigerator 2–8°C Shelf-life: 24 months
Seegene	Anyplex II HPV HR Detection	Thermal Cycler	✗	✓	✗	✓ HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 individually	✓	✗ (5.5 hours)	NR	Batched	Partial Automation	≤-20°C Shelf-life: 13 months
Seegene	Allplex HPV HR Detection	Thermal Cycler	✗	✓	✗	✓ HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 individually	✓	✗ (4 hours)	NR	Batched	Partial Automation	≤-20°C Shelf-life: 13 months
DNA signal amplification (ISH - in situ hybridization)												
QIAGEN	Digene Hybrid Capture 2 High-Risk HPV DNA test	Modular system and Rapid Capture System-RCS	✓	✓	✗	✗	✓	✗ (4 – 5.5 hours)	Low-Med	Batched	Manual	Refrigerator 2–8°C
QIAGEN	careHPV® Test Kit	careHPV Test System	✗	✗	✓ (2018)	✗	✓	✗ (2.5 hours)	Low-Med	Batched	Manual	4–25°C Shelf-life: 12 months
Other HPV DNA tests with full clinical validation [61, 63] according to Meijer/VALGENT criteria (sensitivity, specificity, inter-laboratory agreement and intra-laboratory reproducibility) and published in peer-reviewed literature Contact with manufacturer for full data collection was not possible												
AB Analitica	*REALQUALITY RQ-HPV screen*	*NR*	*NR*	✓	*NR*	✓	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
HPV mRNA tests[8]												
mRNA target amplification (via NASBA - Nucleic Acid Sequence-Based Amplification)												
Hologic	Aptima HPV	Panther	✓	✗	✗	✗ (reflex testing assay allows for subsequent identification of 16/18/45)	✗	✗ (3.5 hours)	High	Random Access	Full automation	2–8°C refrigerated box 15-30°C room temperature box
Validation status provided by manufacturer – full clinical validation according to Meijer/VALGENT criteria (sensitivity, specificity, inter-laboratory agreement and intra-laboratory reproducibility) yet to be published in peer-reviewed literature												
HPV DNA tests												
Atila BioSystems	Ampfire HPV (Geotype 15 hr HPV)	Thermocycler or Powergene 9600 Plus	✗	Full criteria not available yet	✗	✓ HPV 16, 18 individually; other hrHPV pooled (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	✓	✓ (60 minutes)	High	Random Access	Partial Automation	-20°C

HPV tests for primary screening												
Manufacturer	**Assay name**	**Platform**	**Clinical validation** (1)			**HPV 16/18 Genotyping** (2) and additional information	**Self-sampling - vaginal sample** (listed on IFU) (3)	**Test run time (90 minutes or lower)** (4)	**Capacity** (high/med/low throughput) (5)	**Test processing** (batched / random access) (6)	**Level of automation** (full / partial / manual) (7)	**Storage requirements**
			FDA approval	Meijer's Guidelines and/or VALGENT Initiative	WHO Prequalified (year)							
Atila BioSystems	ScreenFire HPV RS Kit	Powergene 9600 Plus Real-Time PCR System	✗	Full criteria not available yet	✗	✓ HPV 16 and HPV18/45 individually; 2 other hrHPV groups: (31/33/35/52/58); and (39/51/56/59/68)	✗	✓ (60 minutes)	High	Batched	Partial Automation	-20°C (4°C and RT also possible for short-term storage) Shelf-life: 12 months
FujireBio	INNO-LiPA™ HPV Genotyping Extra II (Line-probe assay)	NR	✗	Full criteria not available yet	✗	✓ HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 82 individually; other lower risk HPV also reported individually	✓	✗ (NR)	Low-Med	Batched	Partial Automation	Refrigerator 2–8°C
Genefirst	Papilloplex HR HPV DNA Kit	Bio-Rad CFX96 *or* SLAN96P (Need to do DNA extraction before PCR)	✗	Full criteria not available yet	✗	✓ HPV 16, 18, 31, 33, 35 39, 45, 51, 52, 56, 58, 59, 66 and 68 individually	✗	✗ (4 hours)	Med	Batched	Partial Automation	-20°C
Molbio	Truenat HPV-HR	Truelab PCR analyzer	✗	Full criteria not available yet	✗	✓ HPV 16/31 and 18/45	✗	✓ (< 60 minutes)	Low	Random Access	Partial Automation	Room Temperature (2-30◦C) Shelf-life: 24 months
Shanghai ZJ Bio-Tech Co., Ltd. ("Liferiver")	HarmoniaHPV	AutraMic mini4800 Plus	✗	Full criteria not available yet	✗	✓ HPV 16, 18 individually; other hrHPV pooled: (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	✗	✗ (2 hours)	Med	Batched	Full Automation	-20°C

More Information:
(1) Clinical validation criteria are fully described in section 2. Summary of Methods. This Landscape reflects primarily information provided by manufacturers, at a certain point in time, complemented by literature reviews and expert consultations.
(2) HPV 16/18 genotyping refers to the ability of performing partial genotyping and it is described on the "Triage - WHO recommended" section
(3) Some tests and platforms may have external validation for self-sampling, without updating that information on IFU. See also Technology Table 4 - Sampling devices for HPV testing (includes Horizon Scan products)
(4) May be considered for point-of-care or near point-of-care models
(5) 8h capacity: > 300 (high); > 100 - < 300 (med); and <100 (low)
(6) Batched - runs test cases in groups; Random access - may add and run tests individually and at any time
(7) Full automation - primary (or aliquot) specimen added to instrument and no further interaction until result; Partial automation - Primary (or aliquot) specimen added to instrument but requires manual intervention at one or more stages before results are available; Manual - All steps are processed manually, but results may be able to be transferred into IT system automatically
(8) HPV mRNA tests are not recommended for use in women living with HIV because evidence on the outcomes of using HPV mRNA detection applicable to this population was not identified – WHO guidelines-use of mRNA HPV test
FDA - U.S. Food and Drug Administration; HPV - Human Papilloma Virus; IFU - Instructions for use; NR – not reported; WHO - World Health Organization; women living with HIV - Women living with HIV
Note: Products are displayed in alphabetical order from manufacturer name. This Landscape reflects primarily information provided by manufacturers/suppliers, at a certain point in time, complemented by literature reviews and expert consultations.

Technology table 2

Horizon scan for pipeline HPV tests in late stage of development

Horizon scan: HPV tests for primary screening and/or triage – pipeline (not on any market, yet) ("Design Lock" phase AND intends to be available at any market by the end of 2025 AND plans to obtain clinical validation[1])										
Manufacturer	**Assay name**	**Platform**	**Format**	**Genotyping** (2) **HPV 16/18 individually and additional information**	**Self-sampling planned**	**Test run time expected**	**Capacity** (high/med/low throughput) (3)	**Test processing** (batched / random access) (4)	**Level of automation** (full / partial / manual) (5)	**Storage requirements**
HPV DNA tests – pipeline products										
Co-Diagnostics, Inc (Co-Dx) / CoSara Diagnostics	Co-Dx PCR Pro hr-HPV Diagnostic Test	Co-Dx PCR Pro	Real-time PCR	To be defined	✓ (Vaginal Swab)	< 30 min	Low	Single Test	Full	Room Temperature (2-30 ∘C)
Molbio	Truenat HPV HR 16/18 / Truemix HPV HR 16/18	TrueLab PCR analyser / Trueamp automated PCR/Open Real time PCR	Real-time PCR	✓ HPV 16, 18 individually	Planned for 2nd generation – urine	< 60 min	Low on Truelab / Med on Trueamp	Random Access for Truelab and Trueamp / Batched for Open RT-PCR	Partial	Room Temperature (2-30 ∘C) Shelf-life: 24 months
Molbio	Truenat HPV-HR Plus / Truemix HPV HR Plus	TrueLab PCR analyser / Trueamp automated PCR/Open Real time PCR	Real-time PCR	✓ HPV 16, 18 individually; other hrHPV pooled: 31/33/35/45/52/58	Planned for 2nd generation – urine	< 60 min	Low on Truelab / Med on Trueamp	Random Access for Truelab and Trueamp / Batched for Open RT-PCR	Partial	Room Temperature (2-30 ∘C) Shelf-life: 24 months
Molbio	Genotyping	Trueamp automated PCR/Open Real time PCR	Real-time PCR	✓ hrHPV groups: (16/18/33/35); (31/39/45); (51/52/56/58); and (59/66/68)	✗	< 60 min	Low on Trueamp	Random Access on Trueamp/ Batched for Open RT-PCR	Partial	Room Temperature (2-30 ∘C) Shelf-life: 24 months
Pluslife	HPV Card 16/18/45	Mini Dock	Isothermal amplification	✓ HPV 16, 18, 45 individually	✓ (Vaginal Swab)	+/- 30 min	Low (single channel)	Single Test	Full	Room Temperature (2-28∘C) Shelf-life: 13 months
Shanghai ZJ Bio-Tech Co., Ltd. ("Liferiver")	LyoHarmoniaHPV	AutraMic mini4800 Plus ("ChinKing mini")	Real-time PCR	✓ HPV 16, 18 individually	✓ (Vaginal Swab and Urine)	120 min	Med	Batched	Full	Room Temperature (2-30 ∘C)
Shanghai ZJ Bio-Tech Co., Ltd. ("Liferiver")	LyoVenusHPV	AutraMic mini4800 Plus ("ChinKing mini")	Real-time PCR	✓ HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 82 individually;	✓ (Vaginal Swab and Urine)	120 min	Low	Batched	Full	Room Temperature (2-30 ∘C)
SD BioSensor	Standard M10	M10 HPV	Real-time PCR	✓ HPV 16, 18 individually; 6 other HPV groups: (51); (33/52/58); (45/59); (39/68); (56/66)	✓ (Vaginal Swab)	60 min	Low	Random Access	Full	Room Temperature (2-28∘C) Shelf-life: 12 months
Ustar	MultNat HPV 16/18 Assay	MultNAT	Isothermal amplification	✓ HPV 16, 18 individually	✗	40 min	High	Random Access	Full	-25~30°C Shelf-life: 12 months

Horizon scan: HPV tests for primary screening and/or triage – pipeline (not on any market, yet) ("Design Lock" phase AND intends to be available at any market by the end of 2025 AND plans to obtain clinical validation[1])										
Manufacturer	**Assay name**	**Platform**	**Format**	**Genotyping** (2) **HPV 16/18 individually and additional information**	**Self-sampling planned**	**Test run time expected**	**Capacity** (high/med/low throughput) (3)	**Test processing** (batched / random access) (4)	**Level of automation** (full / partial / manual) (5)	**Storage requirements**
Other pipeline HPV DNA tests already with full clinical validation [61, 63] according to Meijer/VALGENT criteria (sensitivity, specificity, inter-laboratory agreement and intra-laboratory reproducibility) and published in peer-reviewed literature Contact with manufacturer for full data collection and analysis was not possible										
Hiantis	OncoPredict HPV Screening	NR	NR	✓	NR	NR	NR	NR	NR	NR
Hiantis	OncoPredict HPV QT	NR	NR	✓	NR	NR	NR	NR	NR	NR
Vitro Master Diagnostica	Vitro HPV HR Detection	NR	NR	✓	NR	NR	NR	NR	NR	NR

More Information:
(1) Clinical validation criteria are fully described in section 2. Summary of Methods.
(2) HPV 16/18 genotyping refers to the ability of performing partial genotyping and it is described on the "Triage - WHO recommended" section
(3) 8h capacity: > 300 (high); > 100 - < 300 (med); and <100 (low)
(4) Batched - runs test cases in groups; Random access - may add and run tests individually and at any time
(5) Full automation - primary (or aliquot) specimen added to instrument and no further interaction until result; Partial automation - Primary (or aliquot) specimen added to instrument but requires manual intervention at one or more stages before results are available; Manual - All steps are processed manually, but results may be able to be transferred into IT system automatically
FDA - U.S. Food and Drug Administration; HPV - Human Papilloma Virus; WHO - World Health Organization; women living with HIV - Women living with HIV
Note: Products are displayed in alphabetical order from manufacturer name. This Landscape reflects primarily information provided by manufacturers/suppliers, at a certain point in time, complemented by literature reviews and expert consultations.

3.1.9 Analysis of the HPV testing technologies landscape

Clinically validated HPV tests

This landscape includes 14 HPV tests (13 HPV DNA and 1 HPV mRNA) with clinical validation and data reported and published in peer-reviewed literature and/or WHO prequalification, according to the criteria presented in Section 2: Summary of Methods. However, it was not possible to obtain a response regarding the REALQUALITY RQ-HPV screen (AB Analitica) for full inclusion and data analysis. Additionally, there 6 HPV DNA tests with reported clinical validation by the manufacturers or academia, however it was not possible to identify publication of full clinical validation with positive outcomes, targeting sensitivity, specificity, inter-laboratory agreement and intra-laboratory reproducibility [61, 63]. The HPV tests with WHO-PQ were all included (four tests in total), although CareHPV Test (Qiagen) failed validation through Meijer/VALGENT criteria, not reaching clinical sensitivity criteria in both studies versus HC2 [64, 65]. Also to note that new tests are entering the market, while others may have been withdrawn. This is the case of NeuMoDx™ HPV Test Strip (QIAGEN), a fully clinically validated test, while the discontinuation of NeuMoDx-96 and NeuMoDx-288 molecular systems was announced in June 2024.

Considering all listed HPV tests with manufacturers' responses, 17 allow at least partial genotyping for HPV 16 and 18, with some tests being able to perform extended partial genotyping for other hrHPV. Regarding validation for use with self-collected samples, 11 tests have self-collection included in their instructions for use (IFUs). However, this also remains an evolving field, with some tests being independently validated for self-collection through certified laboratories or having more formal validation studies underway.

Seven tests can be performed using fully automated sample-to-result platforms, with no or minimal interaction required between sample aliquoting and result, while another ten tests are partially automated, minimizing hands-on time relative to manual tests. Particularly in contexts where differentiated technical human resources are scarce and training can be more challenging, a preference may be given to fully automated platforms. This technical feature is also important in an outreach context, where laboratory personnel and equipment are more restricted.

Turnaround times till the first result differ significantly, with five tests being capable of providing a result within 90 minutes. Long turnaround times are one of multiple factors limiting the test's ability to be used in a single-visit screening model.

Multidisease testing capability is also a relevant feature to accommodate the possibility of using the same platform for different assays. All included technologies are capable of multidisease testing, except for CareHPV Test (Qiagen).

HPV test horizon scan

Twelve HPV DNA tests, shown in technology table 2 have been identified that meet the horizon scan inclusion criteria outlined in Figure 6, of section 2: Summary of Methods. However, it was not possible to obtain responses regarding OncoPredict HPV Screening (Hiantis), OncoPredict HPV QT (Hiantis) and Vitro HPV HR Detection (Vitro Master Diagnostica) for full inclusion and data analysis. These three tests are listed here as they have been already clinically

validated through Meijer/VALGENT criteria [61, 63], with their data published in peer-reviewed literature, acknowledging the importance of validation prior to market introduction.

Some of these pipeline tests are expected to include additional genotypes and/or enhance POC functionality on a second-generation device, and examples include three different assays from Molbio and one from USTAR. Other promising innovations are linked to 'true point-of-care' testing. One example is the Co-Dx PCR Pro hr-HPV Diagnostic Test (Co-Diagnostics, Inc (Co-Dx)), which uses a small and highly portable 'home testing' multiplex platform (no laboratory requirements), linked to a smartphone app, that can provide results in less than 30 minutes and will be able to use self-collected dry samples (see technology table 4 – Sampling devices for HPV testing (includes horizon scan products). The Pluslife HPV Card 16/18/45 utilizes a similar small and highly portable multiplex platform, with an alternative 8 channel, higher throughput analyser also available. A second generation of this test is in development, expected to include additional genotypes and functionalities.

Other products on the horizon include the LyoVenusHPV (designed for triage, not for primary screening) and the LyoHarmoniaHPV assay's (Liferiver) and Standard M10 (SD BioSensor).

Numerous other HPV testing products are on the pipeline, and other innovative and validated solutions are expected in the coming years.

3.1.10 Cost considerations for HPV testing technologies

HPV test price is still one of the main barriers preventing countries from adopting and scaling up HPV testing as the primary screening method. Although HPV testing has proved to be more cost-effective than other alternatives , affordability of the tests for a specific country may vary widely, especially in the context of limited financing for the cervical cancer response.

There are also significant discrepancies in pricing approaches across geographies, variability in distributors' margins, different pricing for public and private sectors and pricing variations, even for the same product, within the same country. Thus, comparisons are very difficult and may be misleading. The variation in pricing may be a result of many factors including:

Inclusiveness: Pricing offers include variable packages of products and services, which often account only for a subset of the total cost of running a test.

Equity: Price equity tends to vary based on test demand or presence of existing infrastructure / platforms to conduct tests.

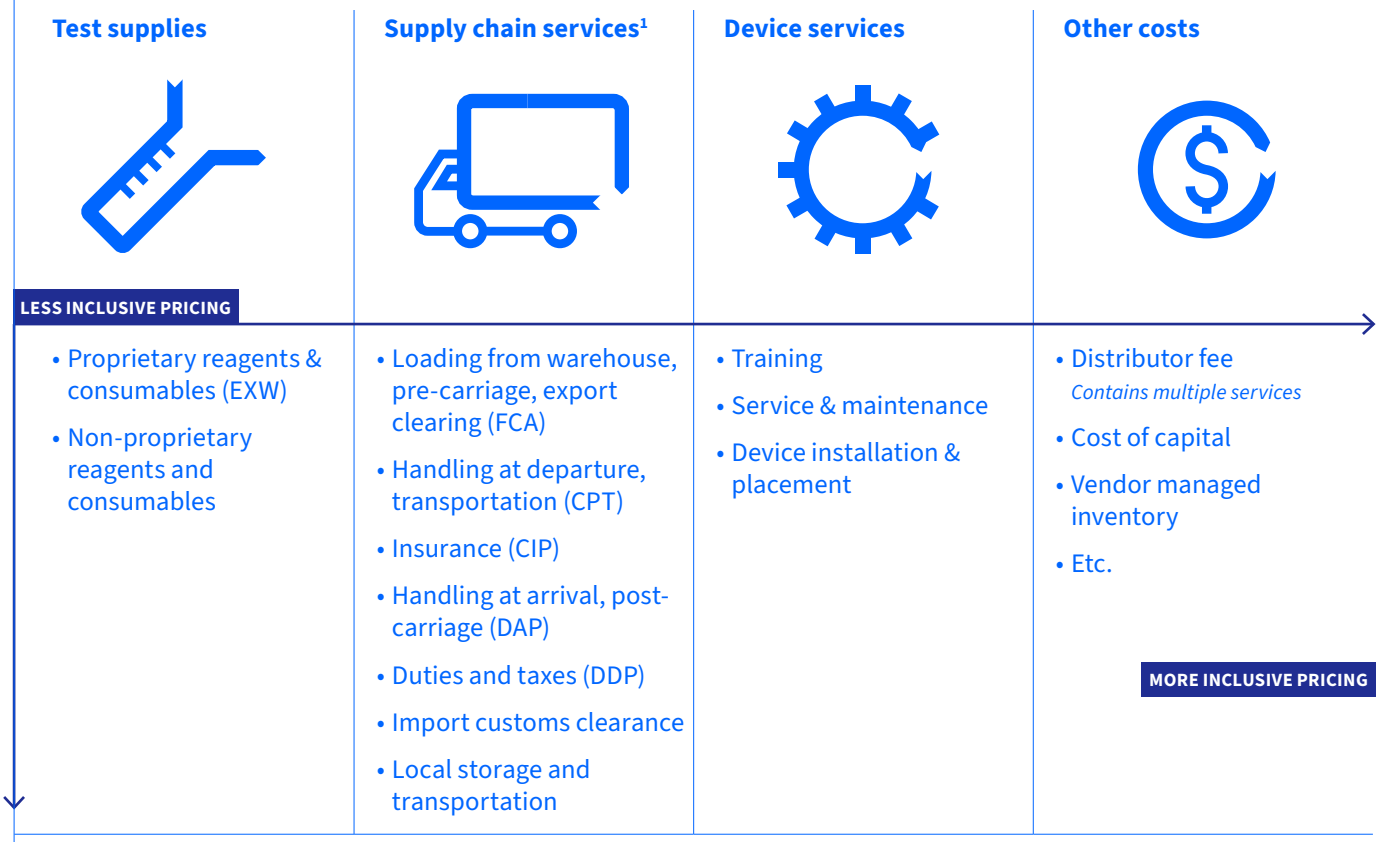
Variability: Other factors include contextual factors, distributor-supplier agreements, access conditions for price agreements (excluding certain procurers, like private sector or limited geographies), etc.

Access: Prices may vary by the procurement or distribution channels being utilized.

Transparency: There is a global need to increase transparency of pricing across suppliers and countries, that all involved stakeholders should pursue to improve procurement practices.

When comparing the costs of different tests, the inclusivity of each pricing offer should be considered. Figure 11 outlines the main cost components for HPV test procurement including test suppliers, supply chain services, support services and other costs.

Figure 11
Main costs components for pricing offers. Source: CHAI, 2022



All-inclusive agreements for molecular tests include proprietary reagents & consumables, training, service & maintenance, and device installation & placement at varying supply chain incoterms

[1] The three-letter incoterms in brackets next to some of these items are a standardized way of denoting specific logistics services and more precise information on each can be found online.

For the sustainable implementation of HPV testing, costs additional to those listed in Figure 11 should also be considered including necessary personnel, ancillary equipment, sample collection products, external quality assurance (EQA) products, specimen referral, laboratory information systems, infrastructure, related treatment supplies, etc. are factors to be considered [60]. These needs and costs will need to be clearly outlined and assessed against existing funding channels [60]. Performance, affordability and accessibility, and operational characteristics of different HPV tests can then all be considered in the purchasing decision.

Figure 12 outlines the main cost considerations for HPV test procurement. However, test selection should not be solely driven by cost, and every decision should be integrated within a specific context, including which service-delivery model is planned and the expected number of tests estimated for a specific timeline.

Figure 12
Main considerations for accessing optimal HPV test pricing

Per-test pricing

- Known, funded demand is key to establish preferential pricing, including testing volumes across various molecular tests for the same supplier
- May depend on volume commitment – consider realistic needs and storage requirements
- Varies based on package of products and services offered, from less inclusive with all components sold separately, to more inclusive agreements see Figure 11
- Costs for additional services should account for what is already paid by other programs
- Final costs heavily influenced by distribution mechanisms, mark-ups and other contextual factors

Access to pricing

- Preferential pricing might be offered to LMICs
- There may be global or regional pricing offers, as well as prices for specific programs/grants, which may be directly accessible or used as reference pricing for local negotiations
- Strict eligibility conditions may apply for certain offers (e.g., volume commitments, payment terms, etc.)
- Agreements may only be accessible by certain buyers or through specific procurement channels or distribution partners

Additional considerations

- Consider leveraging equipment/services in use by other programs (i.e. generic consumables, connectivity, etc.)
- Sample collection device and/or media costs may vary by supplier, consider dry-transport (see 4.5.2. Cost considerations for Sampling Devices and Media)

Given the complexity of price comparisons, the evolving nature of pricing offers (including the expansion or revisions of Global Access Pricing agreements) and the limited availability of pricing information from landscape survey respondents, this document does not include pricing information for products included. At the same time, many HPV testing products are listed in publicly available catalogues, such as the UNICEF Supply Catalogue and the Molecular Diagnostic Pricing Database - African Society for Laboratory Medicine including pricing terms, buyer eligibility and relevant procurement channels for accessing pricing.

For the sustainable implementation of HPV testing, costs additional to those listed in Figure 11 should also be considered including necessary personnel, ancillary equipment, sample collection products, external quality assurance (EQA) products, specimen referral, laboratory information systems, infrastructure, related treatment supplies, etc. are factors to be considered. These needs and costs will need to be clearly outlined and assessed against existing funding channels. Performance, affordability, accessibility and operational characteristics of different HPV tests can then all be considered in the purchasing decision.

RECOMMENDED FOR TRIAGE

3.2 HPV partial and extended genotyping tests

Not all HPV types have the same potential for causing progression to cervical cancer [2]. Thus, different genotypes correspond to different risk levels of infection; detection or lack of detection of high-risk genotypes can aid in identification of clinically important high-grade cervical dysplasia from transient HPV infections. The WHO 2021 guidelines specifically refer to partial genotyping as tests that report separately HPV 16 and 18 (including HPV 45 in some cases) and then other carcinogenic types, and can thus identify women at the highest risk of cervical cancer among those testing positive for HPV [2]. Partial genotyping has shown success as triage tools that can outperform VIA and cytology for triage of women in whom HPV has been detected [66-68].

Most clinically validated HPV tests for primary screening can also support partial genotyping and can be used for triage (see technology table 1).

Other HPV tests may provide extended genotyping, when they report additional types or groups of types, such as HPV31, 33, 35, 45, 52 and 56. However, currently, extended genotyping is not recommended as a triage tool. Thus, a higher number of genotypes presented individually does not necessarily imply that the test is better or more useful for triage. Some of the tests on the market report on specific HPV genotypes separately or collectively as high-risk groups.

3.3 Protein-based biomarkers

High levels of oncoproteins or HPV antibodies can serve as an indicator of precancerous and cancerous lesions. As previously discussed, oncogenic activity can be identified via detection of HPV mRNA transcripts of E6/E7 oncoproteins but can also be identified via direct detection of the oncoproteins themselves, antibodies raised against HPV antigens (HPV16 L1) or oncoprotein-induced DNA methylation.

HPV antibody tests that detect specific IgG antibodies for HPV are also a robustly analyzed form of HPV-blood biomarker testing . Associations have been found between the presence of cervical antibodies and the detection of the concordant HPV DNA type, as well as premalignant lesions, however, there may be a decreased ability to detect serum antibody to HPV overtime due to temporal immune responses [70].

A meta-analysis of 22 performance studies (including four different commercial products and multiple in-house tests) found sensitivity estimates for CIN2+ ranged from 54.2% to 69.5% (none of the tests reached the sensitivity of a HPV clinically validated tests per Meijer criteria), while specificity estimates ranged from 82.8% to 99.1% [71]. These lower sensitivity estimates limit their current utility as a primary screening test, but there may be potential for use as a triage test. Although there are several commercially available oncogenic-biomarker tests, robust clinical translation studies with larger consecutive cohorts of women participants are needed before alternative biomarkers can be recommended even as a triage test to HPV DNA testing. Further evidence regarding performance and real impact on screening programs is still being accumulated.

CURRENTLY NOT RECOMMENDED BY WHO GUIDELINES – INCLUDED AS HORIZON SCAN

3.4 HPV DNA methylation tests

HPV DNA methylation testing is a promising triage option if an assay targeting multiple carcinogenic HPV types is used [72]. DNA methylation has been positively associated with CIN3 across all 12 HPV types, with a multi-12 type methylation assay demonstrating the highest sensitivity (80% vs. 76.6%) and lower test positivity compared to cytology (38.5% vs. 48.7%) – indicating higher specificity [72].

Unlike cytology and other morphological-based tests, HPV DNA methylation does not require cytology infrastructure such as slides of intact cervical cells and is thus more amenable in self-collected specimens [73], however as a triage method, these tests are currently expensive and need further validation. In addition, there may be significant differences in the performance of vaginal vs. cervical samples for methylation markers.

Technology table 3 provides a summary of the main characteristics of the most relevant products within these categories, although not yet recommended by WHO and with very low applicability in the LMIC context, considering the level of technical capacity and resources required.

Technology table 3

Protein-based biomarkers and DNA methylation tests for triage Horizon scan - in late-stage of development and/or ot recommended in the WHO 2021 guidelines

Protein-based biomarkers for triage (excludes HPV mRNA tests and dual-stain)											
Manufacturer	**Assay name**	**Platform**	**Type of assay**	**Test target**	**Type sample (vaginal/cervical/ other)**	**Self-sampling** (listed on IFU)	**Turnaround time/ time to result**	**Capacity** (high/med/low throughput) (1)	**Test processing** (batched / random access) (2)	**Level of automation** (Full / Partial / Manual) (3)	**Storage requirements**
Other protein-based biomarkers											
Arbor Vita	OncoE6™	NA	Lateral flow assay	E6 onco-protein - genotypes HPV16,18	cervical	✗	>90min	N/A	N/A	N/A	No data provided
GaDia SA (5)	PapilloDia	NA	Lateral flow assay – rapid test	Oncoproteins E6 and E7 from HPV 16 and HPV 18	cervical	✗	15 min	Single test	N/A	N/A Manual addition of buffers	5-30 °C
MobiLab (5)	MobiLab HPV 16/18 Antigen Rapid Test	NA	Lateral flow assay – rapid test	HPV 16/18/31 E6 &E7 oncoproteins	Vaginal and cervical	✓ (Delphi self-sampler)	10-15 min	Single test	N/A	N/A Manual addition of buffers	Shelf life- 24 months
DNA methylation											
QIAGEN / Self-screen B.V.	QIAsure Methylation Test / PreCursor-M+	Rotor-Gene Q MDx system / Mic qPCR cycler	PCR	2 Human Genes (FAM19A4 and has-mir124-2)	cervical vaginal	✓	>90min	Low	Random Access	Partial	–30 to –15°C
oncgnostics GmbH	GynTect	Abi7300 or Abi7500 thermalcycler Roche Cobas z480	PCR	6 Methylated Human DNA regions	Cervical	✗	>90min	Low	No data provided	Manual	Refrigerator 2°C to 8°C
oncgnostics GmbH	ScreenYu Gyn	Roche Cobas z480 or BioRad CFX96 Realtime PCR systems	PCR	1 Methylated Human DNA region	Cervical	✗	>90min	Low	No data provided	Manual	Refrigerator 2°C to 8°C

Additional Information:
(1) 8h capacity: > 300 (high); > 100 - < 300 (med); and <100 (low)
(2) Batched - runs test cases in groups; Random access - may add and run tests individually and at any time
(3) Full automation - primary (or aliquot) specimen added to instrument and no further interaction until result; Partial automation - Primary (or aliquot) specimen added to instrument but requires manual intervention at one or more stages before results are available; Manual - All steps are processed manually, but results may be able to be transferred into IT system automatically
(5) Test under development – intended to be used in the future as primary screening test.
NA – Not Applicable; PCR – polymerase chain reaction
Note: Products are displayed in alphabetical order from manufacturer name. This Landscape reflects primarily information provided by manufacturers/suppliers, at a certain point in time, complemented by literature reviews and expert consultations.

4.

Sample collection for HPV testing and emerging self-collection strategies

4.1 Background

The quality of an HPV test is dependent on the quality of the sample taken. Cervical samples for HPV testing are usually obtained during a gynecological exam with a trained health care worker (HCW). However, vaginal self-collection is an important and equally valid option, shown to increase the acceptability of HPV screening.

This section focuses on HPV testing collection media, sampling products and the benefits of different sampling methods, including by a health care worker or by the woman herself. Figure 13 below outlines the relevant sampling elements that should be considered in relation to HPV testing.

Only validated combinations of sampling device, transport conditions and resuspension protocols should be used. Ideally, this would all be included in the product's instructions for use but may have been independently validated by a suitable reference laboratory.

Consumables for HPV testing may be proprietary, specific to the HPV assay supplier or non-proprietary, which are non-specific and able to be paired across various testing products.

Figure 13
Technological components of sample collection. Source: adapted from CHAI

Collection product	Collection type	• Swab vs. Brush • Cervical (HCW-collected) vs vaginal (self-collected)
	Self/HCW regulatory approval	• CE IVD / FDA / WHO PQ product approval for self- vs. HCW-collection
	Dry / wet transport	• Sample transported dry vs. requiring transfer to a transport media
	Stability / transport	• Stability for dry-sample; wet-sample stability dependent on media
Collection media	Regulatory approval	• CE IVD / FDA / WHO PQ / others
	Recommendation by test supplier	• On-label use of media with respective HPV assays
Other	Product use	• Proprietary product for HPV assay supplier only • Non-proprietary, able to be paired across various media/assays
	Costs	• Individual product and kit-specific costs

4.2 Self-sampling

(also known as self-collection)

Self-sampling for HPV testing enables a woman to collect her own vaginal sample for cervical cancer screening without the need for a gynecological examination. This supports new models of care; an outreach model where self-sampling is performed at community site or within the home or one where women self-sample at health care facilities, with access to supportive and knowledgeable health care workers.

Self-collected cervical samples demonstrated equivalent performance to clinician-collected samples for the detection of CIN 2+, provided that a PCR based assay is used [46].

It also improves access to screening, as women may collect vaginal samples by themselves, with no need to go to a health care facility or have a pelvic examination involving the insertion of a speculum. Self-collection can also improve health care services efficiency, by reducing clinician workload, leaving more time for other tasks (task-shifting) [74, 75]. The acceptability and feasibility of self-sampling have been verified in various low-resource settings [41, 75-79]; self-sampling is commonly reported by women as the more appealing option due to increased comfort and privacy, increased efficiency of the testing process and enhanced sense of self-efficacy [80]. The success of self-sampling based screening programs is thus strongly reliant on the empowerment of women through improved health awareness, with the acceptability of self-sampling significantly greater in areas with stronger health education [41].

In 2022, WHO recommendations on self-care interventions were updated, highlighting "where HPV tests are available, programs should consider whether the inclusion of HPV self-sampling as a complementary option within their existing approaches to screening could address gaps in current coverage", and noting that self-sampling can help reach the global target of 70% screening coverage by 2030 (Figure 14) [81]. This WHO brief summarizes how HPV self-sampling works and some considerations for the success of self-sampling implementation. Some countries, such as Australia, Denmark and the Netherlands, have already introduced self-sampling for HPV testing in their national screening programs and several other countries, including LMICs such as Vanuatu, are beginning to leverage self-sampling to overcome screening barriers [82-86]. One of the countries where same-day HPV testing using self-collected specimens has been successfully trialed is Papua New Guinea (PNG) (See case study 1). CHAI, with Unitaid's support, has further helped introduce self-sampling in eight additional countries in the Sub-Sahara African region. For example, in Kenya, CHAI worked with the National Cancer Control Program to roll out community-based HPV self-sampling after realizing women were hesitant to visit facilities due to the risk of COVID-19 exposure [75, 81, 87].

Figure 14
HPV self-sampling for cervical cancer screening infographic.

Source: WHO recommendations on self-care interventions - Human papillomavirus (HPV) self-sampling as part of cervical cancer screening and treatment, 2022 update

Case study 3

Project ROSE, pilot study of self-sampling approach with digital registry support

Malaysia has achieved high-coverage HPV vaccination since 2010, but primary screening coverage within the existing cytology-based program remains low, below 25% [36]. Experts suggest this is partly because Malaysia relies on opportunistic screening, with no registry or follow-up, alongside other factors, including insufficient cytopathologists, lack of space and privacy in care facilities, lack of patient knowledge or time and patient fear or embarrassment [36, 164].

In response to these outcomes, Project ROSE, a collaboration between the University of Malaya, the Malaysian Ministry of Health and the Australian Centre for Prevention of Cervical Cancer (ACPCC), integrates an innovative self-sampling point-of-care model, primary HPV screening and a digital population health registry canSCREEN developed by ACPCC [165].

Self-collected samples for HPV testing were found to be highly acceptable and effective (90% acceptance rates in Project Rose trials) with a high follow up rate when a digital registry was used [36]. Use of efficient communication techniques and digital tracking, including rapid communication of results to patients via mobile phone messages (mHealth), meant women were more likely to screen and return for re-testing follow positive results [36], leading to increased screening uptake and reduced loss to follow up (91% follow-up rate) [36]. Furthermore, 67% of positive patients initiated a call back within the same day of receiving their results [166].

Modelling evaluation found this self-HPV test modality to be more effective and cost-effective than programs without the support of a digital screening registry in Malaysia [36]. Supplementary analysis has further shown that digital registration alone has a substantial effect on the impact and cost-effectiveness of HPV-based screening programs [36]. Without the facilities for recall, much lower compliance rates to follow up would be observed, leading to missed screening and prevention opportunities [36].

Project ROSE highlights several considerations important in the prevention cervical cancer; where clinician-based testing may be a barrier for some women, self-sampling is highly acceptable and effective, provided PCR based testing is used; and screening registries boost screening participation and follow-up, and improve the overall efficacy of screening programs.

4.3 Technologies used for sample collection

(referred by WHO guidelines)

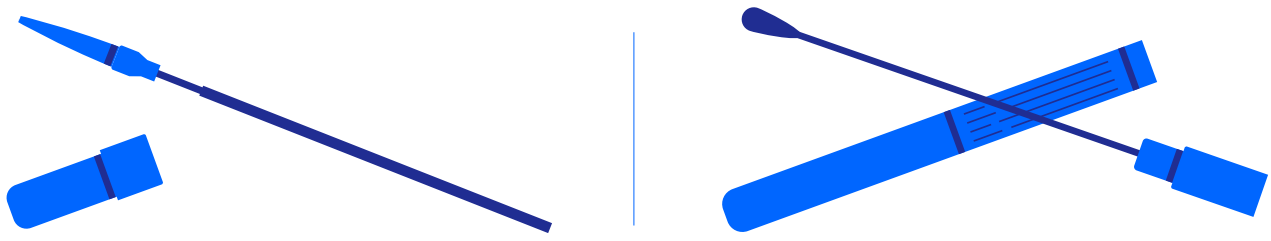
4.3.1 Sample-collection devices

Collection of cervical specimens, either by a clinician or a woman herself, requires high-quality sampling collection devices and media to effectively remove, store and test cellular samples [49].

Self-sampling collection devices are designed to collect vaginal samples and comprise a single-use swab or brush to be inserted into the vagina. Kits generally include a tube to store the swab or brush until laboratory analysis. This might include direct resuspension for on-site testing, a transfer directly into transport medium or transportation dry to store the swab or brush until laboratory analysis proceeds [45]. Once collected, specimens are stable at room temperature for at least 24 hours and some for more than 30 days, depending on the product. Although there are four main types of self-collection devices: swab, brush, lavage and tampon; WHO 2021 guidelines only mention swabs and brushes (Figure 15), given that the data are more limited to support the efficacy for the other type of devices [88].

Figure 15

Example of a brush (on the left side) and a swab (on the right side), that could be used for self-collection.



N.B. These are generic examples. There are multiple types and shapes of brushes and swabs and it is important to consider combined validation between of the HPV test, sample devices and media for transportation or re-suspension.

To optimize self-collection, screening programs should tailor the selection of sampling devices and media to relevant transportation and sampling requirements [45]. For further detailed information on performing these tests, interpretation of results and complementary products necessary when using HPV testing, refer to WHO 2020 Technical guidance and specifications of medical devices for cervical cancer screening.

Of note, HPV tests are only compatible with specific sample collection, storage and transport methods; therefore, selection of a compatible and validated method is essential. Due to compatibility issues, particularly for collection and transport media, there is an urgent need for different HPV tests to validate these various self-collection products and methods. Manufacturers are strongly encouraged to validate self-collection methods, update their IFUs, and submit change notifications acknowledging these sample types.

Sample transportation and storage methods: dry and liquid media

Once collected, a cervical or vaginal sample should be appropriately stored and transported to a testing site. Sample transportation can be via dry transport methods (able to be transported without collection media) or via wet transport (relying on the presence of liquid storage media). However, even dry transportation samples will require resuspension into media prior to analysis on a NAAT testing platform. Extensive stability testing studies have been performed to determine the recommended storage and transportation conditions and shelf-life for different HPV testing assays.

Wet transport refers to the use of a liquid media to transport, store and prepare HPV samples. Once the sample is taken it is stored in a collection tube with the medium and transported to the receiving laboratory [34].

Available transport options include:

- Liquid based cytology media containing alcohol and non-volatile media [89].
- Non-volatile media.
- This media type lyses cells yet maintains nucleic acids and high-sensitivity levels, reducing the need for cell-preservation using liquid-based cytology media that once were used for cytology of self-samples [90].
- Dry transport
    - More recently, HPV assays are allowing for dry transport of the sample to a testing site, avoiding spillage during collection or transportation and providing greater stability of samples.
    - Vaginal self-sampling with a dry swab has been shown to be accurate to detect high-risk HPV infection, compared with both self-collected wet samples and clinician-collected cervical specimens immersed in wet collection medium [91-93].
    - Dry transport thus may assist in the implementation of effective screening strategies in LMICs, in offering the potential for a simplified supply chain, transportation and logistics [46, 89, 91].

Although some media products may be referred as ‘universal’, most are jointly validated with specific devices (and available as kits) and with specific HPV tests and platforms. It is important to look for cross-validated products.

4.3.3 Stability of HCW- and self-collected samples

The stability of cervical samples, ultimately impacting the quality of test performance, can be affected by elements within the whole logistical chain (from collection to testing). Issues in collection methodology, volume and type of collection medium, transport, laboratory handling and choice of cut-offs specific for HPV testing on self-samples can influence testing accuracy.

As new methods of sample collection and transportation emerge, their stability and performance should be evaluated. New findings support the reduction of transport volumes for self-samples [90, 94], with equivalent performance achieved between self-and clinician-collected samples in only 1.5mL of the studied solution (PreservCyt, Hologic) [90]. Dry-transport is also a feasible alternative for transporting at-home self-collected vaginal samples for HPV DNA testing [92].

In terms of the conditions for stability of self-collected samples, optimum storage conditions (in terms of temperature and length of time a sample remains stable) vary by collection medium and test assay. Some dry swabs have demonstrated stability up to at least 7 days at room temperature before stabilization in a solution for resuspension [95, 96], as well as equivalent sensitivity at 2-8°C, 30°C or -20°C when returned to the lab before 29 days [97]. Due to this variability, it is critical to check the required storage conditions of HPV testing assays can support desired health care models.

4.4 Early-stage evaluation technologies for self-sampling

(horizon scan)

Self-care interventions have proven to strength health care services and improve universal health coverage. Thus, there has been a global effort to develop self-sampling solutions that are accurate, less invasive, adaptable to different contexts and compatible with HPV testing, helping to overcome multiple barriers related to cervical screening. However, the products listed in this horizon scan section are still under evaluation/validation and not yet recommended and/or commercially available.

4.4.1 Urine self-collection devices

Included as horizon scan

Clinician and self-sampled first-void urine testing are being evaluated as potentially non-invasive cervical cancer screening methods; however, these are not yet recommended for HPV screening [2, 98, 99].

First-void urine has been shown to contain higher concentrations of sexually transmitted infections (STI)-related DNA, [87] (including those of HPV), and thus urine sampling offers an opportunity for multiplexed testing across a wider range of STIs. Urine sampling is a non-invasive method, which, similarly to self-collected vaginal samples, may increase acceptability. Like other types of self-sampling methods, urine self-collection reduces the need for pelvic examination, which in addition to the reduced human resources need, have also the potential to lower overall screening costs due to the lack of a requirement for a speculum [46, 98, 100].

Although implementation benefits are clear, performance data on sensitivity and specificity remain limited and do not demonstrate equivalent performance to vaginal self-samples limited to date [98, 101]. A meta-analysis of 15 studies inclusive of over 3400 women, using HPV DNA tests, demonstrated pooled sensitivity for high-risk HPV detection in urine of 78% (70-84%) and specificity of 89% (81-94%), demonstrating the accuracy of HPV detection in urine but also the need for further improvement and evaluation [101].

There is also a need to optimize and standardize sampling, storage and processing methods of urine samples, including preventing DNA degradation during extraction, recovering cell-free HPV DNA in addition to cell-associated DNA and ensuring sufficient volume of first-void urine [102]. HPV prevalence data based on urine samples collected, stored and processed under suboptimal conditions may underestimate HPV infection rates [102].

The Validation of Human Papillomavirus Assays and Collection Devices for Self-samples and Urine Samples (VALHUDES) study will assess accuracy of HPV testing on first-void urine and vaginal self-collected samples and compare with the same HPV assay applied on a cervical liquid-based cytology sample collected by a trained clinician [74, 103]. However, this trial exclusively utilizes a specific proprietary urine collection device, which may be difficult to replicate in many LMIC settings, because of associated costs [74, 104].

4.5 Sampling devices for HPV testing landscape

This landscape report presents an overview of the currently available sample collection devices, with focus on brushes and swabs for HCW-collected and self-sampling. According to inclusion criteria presented previously (see section 2. Summary of Methods), the horizon scan presents a list of products that might be of value in the future, not currently recommended or available, though. The main features of sampling technologies are presented on technology table 4.

Technology table 4

Sampling devices for HPV testing (includes horizon scan products)

Sampling devices for HPV tests								
Manufacturer	**Product name**	**HPV assay compatibility**	**Type of device (brush/ swab/other) and type of sample (vaginal/cervical/ other)**	**Designed for self-collection (1)**	**Possible package configuration**	**Compatible for dry transportation** (on IFU)	**Compatible with other tests** (CT, NG, TV, others) (on IFU)	**Sample stability**
Referred in WHO guidelines – Swabs and Brushes								
Abbott Molecular	Abbott Multi-collect Specimen Collection Kit	RealTime HR HPV (Abbott)	Swab – vaginal and cervical	✓ (under VALHUDES validation)	Full kit with transport media	✗	✓ (CT/NG)	No data provided
Abbott Molecular	Abbott Multi-collect Specimen Collection Kit	Alinity m HR HPV (Abbott)	Swab – vaginal	✓ (validated - VALHUDES)	Full kit with transport media	✗	✓ (CT/NG/TV/ others)	After collection, transport and store transport tube at 2 to 30°C for up to 14 days and -25°C to -15°C for up to 6 months
Abbott Molecular	Abbott Cervi-collect Specimen Collection Kit	RealTime HR HPV (Abbott)	Brush – cervical	✗	Full kit with transport media	✗	✗	After collection, transport and store transport tube at 2°C to 30°C for up to 14 days. If longer storage is needed, store at -10°C or below for up to 90 days.
Abbott Molecular	Alinity m Cervi-collect Specimen Collection Kit	Alinity m HR HPV (Abbott)	Brush – cervical	✗	Full kit with transport media	✗	✗	After collection, transport and store transport tube at 2°C to 30°C for up to 6 months and –20 ± 5°C for up to 6 months.
Aprovix AB	Qvintip™	RealTime HR HPV (Abbott), Cobas 4800 and 6800 (Roche), BD Onclarity HPV Assay (BD), Xpert HPV (Cepheid) and Anyplex II HPV HR Detection (Seegene)	Swab – vaginal	✓ (under VALHUDES validation)	Device alone or Full kit with sample transport tube	✓	Validation ongoing	Transport at ambient temperature avoiding direct sunlight and storage as dry sample at 20-25°C without high humidity for up to 4 weeks after sampling. Sample stability for wet-transport and wet storage dependent on media used.
Atila	Atila Cervical Sampling Device	No data provided	Swab – vaginal	✓ (validated - IFU)	Device alone or Full kit with transport media	✓	✓ (CT/NG/TV/ others)	No data provided
Copan Italia Spa, Brescia, Italy	L-shaped/Cone Shaped FLOQ Swabs	Cobas 4800 HPV (Roche), RealTime HR HPV (Abbott), Anyplex II HPV HR Detection assay (Seegene)	Swab – cervical	✗	Device alone or Full kit with transport media	✓	✓ (CT/NG/TV/ others)	Samples can be assayed at least 14 days from time of sample collection (-20 to +50 °C) if used as a dry swab. Sample stability for wet-transport dependent on media used.
Copan Flock Technologies SRL, part of Copan Diagnostics Inc.	Self Vaginal FLOQSwabs™	Xpert HPV test (Cepheid), Anyplex ll HPV HR Detection assay (Seegene); Cobas 4800 and 5800/6800/8800 (Roche), BD Onclarity HPV Assay (BD) – *on label*, RealTime HR HPV (Abbott), Alinity m HR HPV (Abbott)	Swab – vaginal and cervical	✓ (validated – IFU)	Device alone or Full kit with transport media	✓	✓ (CT/NG/TV/ others)	14 days from time of sample collection (15- 25°C) if used as a dry-swab. Sample stability for wet-transport dependent on media used
Hologic Gen-Prob, Inc	Aptima Cervical Specimen Collection and Transport Kit	Aptima (Hologic)	Brush – cervical	✗	Full kit with transport media	✗	✗	Stable at 2°C to 30°C until tested. Specimens should be assayed within 60 days of collection. If longer storage is needed, cervical specimen transport tubes may be stored at ≤ –20°C for up to 24 months after collection.

Sampling devices for HPV tests								
Manufacturer	**Product name**	**HPV assay compatibility**	**Type of device (brush/ swab/other) and type of sample (vaginal/cervical/ other)**	**Designed for self-collection (1)**	**Possible package configuration**	**Compatible for dry transportation** (on IFU)	**Compatible with other tests** (CT, NG, TV, others) (on IFU)	**Sample stability**
Non-proprietary product Generic (Dacron cotton Swab)	Plain Sterile Swab in PreservCyt (PC)	Cobas 4800 and 5800/6800/8800 (Roche), RealTime HR HPV (Abbott)	Swab – vaginal	✓ (validated - IFU)	Device alone or kit with transport media	✗	✗	Within 3 weeks from sample collection
Qiagen	careBrush®	careHPV (QIAGEN)	Brush –vaginal and cervical	✓ (validated - IFU)	Full kit with transport media	✗	✗	Specimens collected at room temperature (15-30°C) for 14 days or 2-8°C for 30 days
Roche	Roche Cervical Collection Brush (Bulk)	Cobas 4800 and 5800/6800/8800 (Roche)	Swab – cervical	✗	Device alone	✗	✓ (CT/NG)	Transport at 2-30◦C and stable within 90 days
Roche	Roche Cervical Collection Brush (Sterile)	Cobas 4800 and 5800/6800/8800 (Roche)	Swab – cervical	✗	Device alone	✗	✓ (CT/NG)	Transport at 2-30◦C and stable within 90 days
Rovers Medical Devices	Cervex Brush-Combi	BD Onclarity HPV Assay (BD), Alinity m HR HPV (Abbott), RealTime HR HPV (Abbott), Xpert HPV test (Cepheid), Papilloplex HR HPV DNA Kit (Genefirst), NeuMoDx™ HPV Test Strip, careHPV and Digene Hybrid Capture 2 High-Risk HPV DNA test (QIAGEN), Cobas 4800 and 5800/6800/8800 (Roche), Anyplex ll HPV HR Detection assay and Allplex HPV HR Detection (Seegene); HPV Risk Assay (Self-screen); HarmoniaHPV and VenusHPV (“Liferiver”), Aptima (Hologic)	Brush – cervical	✗	Device alone	✗	✗	No data provided
Rovers Medical Devices	Evalyn Brush®	BD Onclarity HPV Assay (BD)	Brush – vaginal	✓ (validated - VALHUDES)	Device alone with transportation tube or Full kit with transport media	✓	✗	Analytically stable with respect to human genomic material and HPV detection for up to 32 weeks at temperatures ranging from 4 °C to 30 °C.
Rovers Medical Devices	Viba Brush®	NR	Brush – vaginal	✓ (under VALHUDES validation)	Device Alone with transportation tube	✓	✗	24-48hrs
Horizon scan – not yet recommended and/or commercially available								
Cervical or vaginal sampling – other than swabs/brushes								
Rovers Medical Devices	Delphi Vaginal Self Sampler	NR	Lavage Sampler – vaginal and cervical	✓	Full kit with transport media	NA	✗	Send the samples collected within 24 hours (storage temp 5-40°C). Store specimens in sample vial for up to 5 days at 5–40 °C. Specimen storage and transport should not exceed 5 days at 5–40 °C or 180 days frozen at -20 °C

Sampling devices for HPV tests								
Manufacturer	**Product name**	**HPV assay compatibility**	**Type of device (brush/ swab/other) and type of sample (vaginal/cervical/ other)**	**Designed for self-collection (1)**	**Possible package configuration**	**Compatible for dry transportation** (on IFU)	**Compatible with other tests** (CT, NG, TV, others) (on IFU)	**Sample stability**
V-Veil-Up Production SRL	V-Veil UP2	Anyplex II HPV HR Detection assay (Seegene), Papilloplex High Risk HPV (GeneFirst)	vaginal Collector veil – vaginal	✓	Device alone *or* Kit 1.1: Include a dry/empty conical tube to transport the sample *or* Kit 2.1 and 3.1: Include a tube of transport and fixative solution	✓	✓ (CT/NG/TV/ others)	Inside the liquid, the sample has a shelf life of 83 days outside the refrigerator. 30 days with dry tube
Urine sampling								
Copan Italia Spa, Brescia, Italy	Self UriSponge	Anyplex II HPV HR Detection assay (Seegene)	Sponge – urine	✓	Device alone	NA	✓ (CT/NG/TV/ others)	Specimens may be refrigerated at 2-8°C and processed within 3 weeks or stored at room temperature (20-25°C) and processed within 1 week
Novosanis	Colli-Pee	RealTime HR HPV (Abbott) and other pilot studies for Cobas 4800 and 5800/6800/8800 (Roche), BD Onclarity HPV Assay (BD), Aptima (Hologic), Xpert HPV test (Cepheid), Papilloplex (Genefirst), Anyplex II HPV HR (Seegene)	Collector tube – urine	✓	Device alone	NA	✗ (may be used to collect urine for other STI testing in men)	UCM™ - 7 days ambient temperatures UAS™ - 7 days ambient temperatures
Swabs/brushes in late-stage development (pipeline products – not commercially available)								
Sherlock Biosciences	In development collection device for high-risk HPV assay	High Risk HPV Strain Detection – Lateral flow assay under development	Dry swab with buffer-containing transfer device – vaginal	✓	Full kit with transport media	✓	✗	Room temperature storage, target of >18 months
Co-Diagnostics, Inc (Co-Dx)	In development collection device for Co-Dx PCR Pro hr-HPV test	Co-Dx PCR Pro (2)	Dry swab – vaginal or cervical Cup – urine	✓	Full kit	✓ NA	In development	Goal is room temperature storage up to 1 year, but stability studies need to be completed.

Additional Information:
(1) Self-collection validation may be not for HPV testing platforms claimed as compatible
(2) See Technology Table 2 - Horizon scan for pipeline HPV tests in late stage of development
CT - Chlamydia trachomatis; FDA - U.S. Food and Drug Administration; HPV - Human Papilloma Virus; IFU - Instructions for use; NA – not applicable; NG - Neisseria gonorrhoeae; NR – not reported; TV - Trichomonas vaginalis; WHO - World Health Organization; women living with HIV - Women living with HIV.
Note: Products are displayed in alphabetical order from manufacturer name. This Landscape reflects primarily information provided by manufacturers/suppliers, at a certain point in time, complemented by literature reviews and expert consultations.

4.5.1 Analysis of the sampling devices landscape

There is a variety of swabs and brushes for collecting samples for HPV testing, including through self-collection, using vaginal samples. However, it is important to acknowledge that there is a need for formal validation for this specific indication, as the device may be validated for self-collection with other tests, but not for HPV detection. Ideally such information should be incorporated on the device IFU or in the IFU of the HPV test used with the device.

The majority of sample collection devices are either swabs or brushes, with 6 swabs and 3 brushes designed for self-collection, using vaginal samples.

Stability of the samples (self or clinician-collected) will depend on multiple factors, including type of transportation, wet or dry. If wet transportation is need, suitable transport media is required, and this is generally provided within the kit. External conditions, such as humidity and temperature should also be controlled within the limits articulated in the IFU or validation study. Dry transportation may be very convenient in multiple situations.

Design of the devices may vary, however performance, validation and usability within the specific setting should be prioritized.

In the horizon scan, different devices are presented, including for collection of urine, as well as innovative methods for collection of vaginal samples. The specific role of these products is yet to be fully understood and validated.

4.5.2 Cost considerations for sampling devices and media

When comparing different sampling devices some practical aspects should be considered, as they may impact costs and test performance:

- Compatibility and cross validation between HPV tests, testing, sampling devices and transport and re-suspension methods (including media);
- Possibility of purchasing full kits or devices and medium/buffer separately. If kits are available, configurations may differ;
- Pricing may depend on volume – consider realistic needs and storage requirements;
- Consider leveraging other programs, that may use similar and compatible products;
- Possibility of dry transportation;
- Purchasing from in-country distributors may lead to higher costs compared to direct from suppliers or pooled procurement mechanisms
- Each medium may contain different “preservatives”, that may interfere with the ability to be used and shipped in certain circumstances (e.g., alcohol is a flammable component, and high quantities may impose a relevant risk, being prohibited in some conditions; guanidine-based products cannot be shipped by post by some countries, such as USA, as its compounds can decompose to highly toxic hydrogen cyanide gas);
- Consumables costs associated with self-collection should not be neglected when planning a sustainable program.

5.
Cytology-based testing

Cytology-based testing has been recognized as effective in reducing cervical cancer incidence and deaths when implemented in national programs with high and ongoing quality assurance measures, high coverage of at-risk female populations and adequate resources for follow-up (colposcopy, pathology and treatment) [2, 105, 106]. This includes computer-assisted cytology systems, and more recently, artificial AI-enhanced cytology systems that support automated evaluation of cytology slides and are currently being implemented in HICs [107].

Cytology tests (including the conventional Papanicolaou (Pap) smear test, liquid-based cytology (LBC) and now dual staining techniques) identify atypical cells on the cervix using microscopy on a cellular cervix sample by a trained expert [108].

RECOMMENDED FOR TRIAGE

Can be used for PRIMARY SCREENING in existing programs with quality assurance, until HPV screening is operational, according to WHO 2021 guidelines [2]

5.1 Cytology: Pap smear, liquid-based and computer assisted

Cytology tests are more specific than HPV tests (96% for LBC vs 72% for HPV testing) for the detection of biopsy confirmed CIN2+, so are ideal for triaging in high-income contexts [109].

Automated cytology systems, using computer-based scanning of cytology slides have demonstrated equivalent performance as conventional cytology [110], and may increase the efficiency of cytology testing in high-resource settings [107].

Cytology testing is less suitable for LMICs however, due to significant resource requirements [2, 111, 112]. Cytology is expensive, time-consuming and a technically demanding test requiring highly-trained technicians, ongoing intensive quality assurance and a substantial amount of laboratory equipment [50, 52]. Cytology processing can involve several days to weeks for results, making it inappropriate for campaign or point-of-care testing models; cytology relies on multiple visits to health care providers/clinics, close client/practitioner follow-up, highly-trained health care professionals and a developed quality assurance program [2, 50, 52, 111, 112]. In areas where laboratory or skilled labor resources are unavailable, cytology has shown sub-optimal sensitivity and false negative results due to sampling problems or interpretation error [2]. However, where resources are available, LBC triage achieves greater clinical accuracy than VIA triage and is thus preferred, in combination with HPV testing [109].

Sample collection and transport

Cytology involves collecting exfoliated cells from the transformational zone (TZ) of the cervix and fixing them to a slide (conventional cytology) or making a suspension of cells in liquid media. Either way, sample should be collected by a trained health care worker, during pelvic examination with a speculum. It requires the use of appropriate collection devices, typically a cervical broom or spatula in combination with a cytobrush, to reduce the proportion of unsatisfactory smears that lead to misdiagnosis [107].

Aside from typical consumables required for cervical examinations, including gloves (disposable or sterile reusable), cotton balls and cotton swab, saline solution as a cleaning agent and lubricating jelly, the following commodities are required for cytology:

- Sampling device, such as, cervical broom, endocervical brush, plastic spatula, cervix brush combi
- Speculum
- Clean glass slides, glass marking pencil, hanging drop slide and glass coverslips, fixative solution spray and histology containers – *for conventional cytology*
- LBC vial containing fixative – *for LBC*
- Mailing containers such as specimen biohazard bags

See Pap Smear Collection and Preparation: Key Points for more for detailed information on clinical examination, consumables and equipment required [113].

After cervical sampling, LBC requires fewer and more simple steps, resulting in better sample quality and readability and a reduced proportion of unsatisfactory slides, when compared with conventional cytology [26]. A disadvantage of LBC is the high cost of the equipment and consumables required for established LBC methods, creating a barrier for use in resource-constrained settings [26].

Materials for LBC are available through commercial, automated preparation systems. However, manual methods for LBC may be less expensive than commercial LBC systems and a potential alternative for low-resource settings [26].

Computer-assisted cytology

The ThinPrep Imaging System (TIS) has been available since 2003, when it was first approved by FDA, and is an automated imaging and review system for use with ThinPrep Pap Test slides. It combines imaging technology to identify microscopic fields of diagnostic interest with automated stage movement of a microscope in order to locate these fields. In routine use, the ThinPrep Imaging System selects 22 fields of view for a Cytotechnologist to review. Following a review of these fields, the cytotechnologist will either complete the diagnosis if no abnormalities are identified or review the entire slide if any abnormalities are identified. The ThinPrep Imaging System also allows the physical marking of locations of interest for the cytopathologist. These systems have been in widespread use in high resource settings, with the major advantage being that cytotechnologist efficiency is significantly improved.

The Genius™ Digital Diagnostics System (ThinPrep, Hologic) is the more recently available product in this category. Genius Digital Diagnostics combines a new AI algorithm with advanced volumetric imaging technology to help cytotechnologists and pathologists identify pre-cancerous lesions and cancer cells. The system can rapidly analyze all cells on a ThinPrep® Pap test digital image, presenting an AI-generated gallery of the most diagnostically relevant images on a PC screen. Cytotechnologists and pathologists review images on a computer screen and most cases can be reported without the need for a microscope, using just the scanned image of the slide. The system is CE-marked (https://www.hologic.com/hologic-products/cytology/genius-digital-diagnostics-system).

Another computer-assisted cytology system, with AI-based algorithm, is miLab™ CER (Noul Co., Ltd), which presents cytologic results on a slide-by-slide basis according to Bethesda system classification. A final review and confirmation by the user are still required. The system is CE-IVD approved and is currently running external validation.

5.2 Dual-stain cytology for p16 and Ki-67

Dual stain testing is a newer triage tool, already available in some high-income settings for triage, following a positive HPV test and recently recommended in WHO guidelines for use of dual-stain cytology (June 2024) [114]. Dual staining measures the presence of two proteins (p16 and Ki-67) that, when co-expressed in a single cell, are highly specific indicators of precancerous lesion development. The WHO Guidelines Development Group (GDG) reviewed the available evidence, analyzed women's preferences and through mathematical modelling, using the Policy1-Cervix platform (developed by the Daffodil Centre), predicted the outcomes of using this triage tool in the general population across 78 LMICs. In a screen, triage and treat approach, currently WHO considers dual-stain cytology as a possible alternative to triage of women from the general population, after a positive HPV test. When providing dual-stain cytology to triage women after a positive HPV NAT, WHO suggests using samples collected by the health worker, as dual-stain cytology has not yet been validated in self-collected samples; and retesting with HPV NAT 24 months after a negative dual-stain cytology result. However, these are conditional recommendations based on low-certainty evidence for dual-stain cytology as a triage test. No recommendation was made for using dual-stain cytology to triage women living with HIV after a positive HPV DNA test, because evidence on the outcomes of using dual-stain cytology applicable to this population was minimal. [114]

As a cytological method, dual stain requires complex laboratory infrastructure (including immunostaining infrastructure), specific reagents and consumables, training and resources for dual stain interpretation, and ongoing quality assurance programs. Dual-stain cytology has been developed and validated

for LBC slides, not for conventional Pap smears, so it requires all the LBC infrastructure, as well as for immunostaining. These specific features constrain its wide implementation, so its use could only be considered within a health system that ensures adequate laboratory infrastructure, quality assurance, management and monitoring of follow-up testing for those referred to 24-month follow-up surveillance with HPV test after a negative dual-stain result. Manual dual stain has a subjective component, requiring a cytotechnologist to look at the slide to determine the results [115]. Novel automated AI-based approaches to dual stain (see Figure 16 as an example) removes the reliance on human interpretation and, with further evaluation, may exceed the performance of manual techniques [115, 116]; AI-based dual stain has shown lower rates of positivity than cytology and manual dual stain ($p<0.001$), with equivalent sensitivity and substantially higher specificity compared with both Pap and manual DS ($p<0.001$) [116]. As per AI-based visual assessment tools, extensive validation and feasibility evaluation is needed before consideration as a recommended approach.

This landscape identifies one immunohistochemistry assay for simultaneous qualitative detection of p16 and Ki-67, which is the CINtec® PLUS Cytology (Roche), approved for use as a triage tool (*Technology Table 5*).

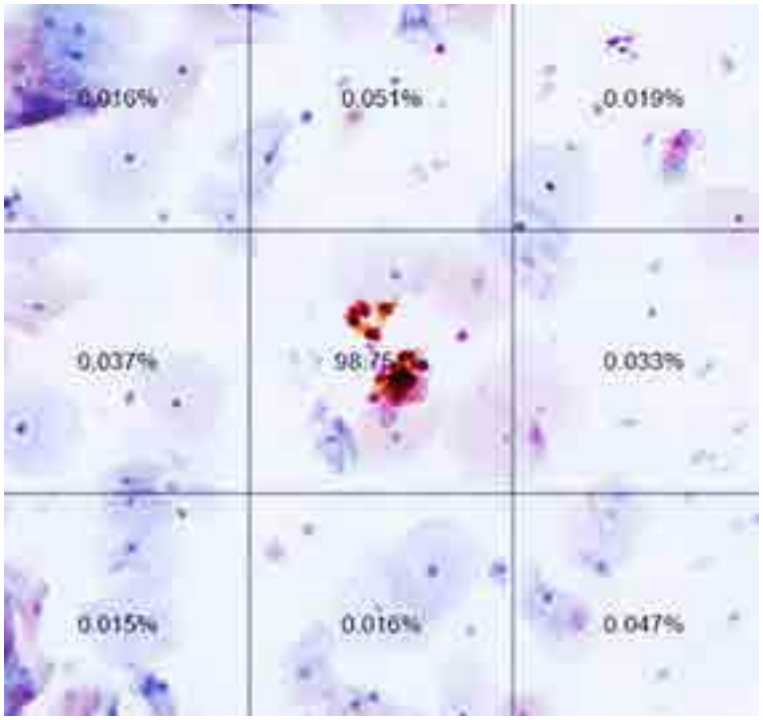


Figure 16
A slide from an automated dual stain cytology test. The percentages are AI-generated likelihoods of positive results. The image at centre (labelled 98.75%) shows a positive result. Nicolas Wentzensen, M.D., Ph.D.

Source: www.nih.gov

Technology table 5

Dual-stain cytology for detection of p16 and Ki-67

Dual-stain cytology (p16/Ki-67) (1)							
Manufacturer	**Assay name**	**Platform**	**Type of assay**	**Test target**	**Type sample**	**Self-sampling**	**Storage requirements**
Roche	CINtec® PLUS Cytology test	BenchMark GX/ XT/ ULTRA	Immunocytochemistry	$p16^{INK4a}$ and Ki-67	cervical	✗	Refrigerator 2°C to 8°C

(1) Dual-stain cytology is not recommended for use in women living with HIV because evidence on the outcomes of using dual-stain cytology applicable to this population was minimal – WHO dual-stain cytology guidelines

6.

Visual assessment techniques

RECOMMENDED FOR TRIAGE

6.1 Colposcopy

Colposcopy involves magnification and illumination of the vulva, vaginal walls and cervix, using acetic acid wash and a light-illuminated, stereoscopic binocular microscope – a colposcope. Colposcopy is performed after a positive HPV test and when the cytology or the cervix appearance is abnormal, to assess whether ablative or excisional therapy is appropriate, and facilitate precise biopsy and treatment where necessary [26]. Colposcopy does not perform well for primary screening [26], however is an effective diagnostic tool for women with a positive primary screening test or for symptomatic women.

As with VIA, new optical techniques, including camera-enhanced image capture or magnification, are under development. These may enhance the accuracy of colposcopy as a triage tool.

When performed in a competent quality-assured service, colposcopy has important advantages, particularly for women with endocervical or glandular disease, very large lesions or suspicion of invasive disease. As a visual assessment technology, colposcopy is more accurate and associated with less variability than VIA, due to the use of microscopy.

Limitations to traditional colposcopy

Existing challenges for the application of colposcopy in LMICs include: the need for well-trained and experienced colposcopists; dependence on the subjective interpretation of colposcopists, leading to inter- and intra-colposcopists variabilities; challenges to adequate visualization of the cervix from environmental factors or inflamed or obscured cell lining; strict diagnostic standards and quality control that are unable to be followed by inexperienced colposcopists, leading to discrepant reporting and results interpretation [24]. Inaccurate impressions can lead to over- and under-treatment of HPV+ women compared to a histopathological reference standard [25].

Aside from typical consumables required for the cervical examinations already mentioned, the following commodities are uniquely required for colposcopy testing:

- Colposcope
- Camera system
- Computerized data management system
- Well-trained colposcopist and skilled attendants
- Tissue sampling instruments
- Biopsy forceps and local analgesia syringes (if biopsy is needed)

(See the IARC 2022 handbook on cervical cancer prevention [26] for detailed information on the equipment required).

RECOMMENDED FOR TRIAGE

Programs using VIA as the PRIMARY SCREENING should transition rapidly to HPV testing because of the inherent challenges with quality assurance, according to WHO 2021 guidelines [2]

6.2 Visual inspection with acetic acid (VIA)

Visual techniques used in cervical screening include a naked eye examination with acetic acid (VIA) or Lugol's iodine (VILI). Digital imaging tools are also being developed to improve the performance of visual inspection methods (e.g., digital cervicography, smartphone attachments, intra-vaginal endoscopes or portable digital colposcopes). To date, no results of large, randomized control trials (RCTs) have been published that enable objective assessment of the effectiveness of enhanced VIA systems to detect precancer compared with routine VIA, and they are therefore not yet officially recommended for use as a triage tool. Further evaluation of clinical effectiveness is needed before integration of these technologies into national cervical screening programs.

Visual inspection with acetic acid (VIA) or with Lugol's iodine (VILI)

VIA or VILI is a simple test for the early detection of cervical precancerous lesions approved by WHO as either a triaging tool or as a tool for assessment for eligibility of ablative treatment in HPV-positive women.

The quality of naked-eye visual inspection tools is provider/clinician dependent (subjective), leading to significant variations in sensitivity, specificity and overall effectiveness [3, 117, 118]. Visual inspection methods are also not appropriate for use in women when the transformation zone is no longer visible, including post-menopausal women [2], as lesions are likely to be missed in this setting . Even in younger women, transformation zone may not be visible. In a screening program in Nigeria, amongst women as young as age 30, the transformative zone was only partially visible in 8.3% and not visible in 23.1% of women (31.5% total), rising to 12.5 and 52.1% (64.6% total) by age 49 years.

The main commodities needed for VIA are inexpensive (vinegar and cotton). However, the inaccuracies of VIA, and the need for extensive service provider training as well as ongoing quality control and quality assurance [26, 117, 119] should be borne in mind.

Aside from typical consumables required for cervical examinations already mentioned, the following commodities are uniquely required for VIA/VILI testing:

- Dilute acetic acid (3-5%) solution or Lugol's iodine solution
- Digital or other magnification devices to assist visual examination [120]

See the IARC atlas on VIA for more detailed information on examination consumables and equipment required.

6.3 Enhanced visual assessment (EVA) tools

These technologies aim to improve visual methods used in cervical screening and triage. This enhancement of visualization and improved interpretation of images aims to improve performance and reduce variability of results between operators. Although digital colposcopy is being used more broadly, AI-based systems are still under development and evaluation, not recommended in WHO 2021 guidelines algorithms.

6.3.1 Digital colposcopy

New portable digital colposcopes can be used to alleviate the "colposcopy bottleneck" and improve the accuracy of colposcopy-based screen-and-triage programs [24, 25]. Since they are often integrated with artificial intelligence software, some current examples of digital colposcopes are listed and described below.

Digital colposcopes allow for ultra-high-resolution imaging of the cervix, which can be magnified to higher degrees than a standard colposcope and thus permit enhanced visualization of cervical surface morphology and increased triage efficacy. Evidence suggests digital colposcopy may be an effective tool; with similar or even increased CIN detection, compared with standard colposcopy [121] and other potential advantages, like encouraging patient engagement, by allowing them to see their images of their own body [122], electronic documentation and remote decision report, allowing discussion and continuous learning.

These technologies offer portability, low energy consumption, lower costs than traditional colposcopes and the ability for widespread use, including in rural or outreach contexts [123, 124]. Implementation of digital colposcopes may thus not require extensive infrastructure investment as they can leverage existing mobile health devices for colposcopy grade imaging and be supported by external expertise or even AI-based algorithms [125, 126].

However, the quality of imaging and consequently the performance, may vary between devices, which have different specifications [126]. The resolution of the camera is of high importance, and well as its ability to magnify the images without distortion. The optical zoom is related to the lens of the camera, while the digital zoom crops the image, reducing its resolution and quality.

Main features of digital colposcopes included in this landscape are summarized in Technology Table 5 and Technology Table 6 and 7.

To note that the Gynocular (Gynius Plus AB), although included in this section, was developed initially as a non-digital portable colposcope, and currently also has the ability to be coupled with a smartphone (iOS or Android based) and allow digital colposcopy.

6.3.2 Artificial intelligence (AI)-enhanced visual evaluation and opto-electrical tools

New AI-based screening technologies using deep learning machine algorithms have been in development, aiming to improve the accuracy, accessibility and efficiency of secondary prevention tools.

Deep learning is a machine learning method that applies pattern recognition and other different characteristics (e.g., texture, edges and curves), to make a stratification of the cases, which allow a 'risk-based' screening strategy [127]. Most AI-based algorithms evaluate cervical images taken through digital colposcopy or other image capture devices, while others may use different features, through optical and electrical evaluation of the cervix, detecting oncological changes at the cellular level without the need for a digital photograph [128]. As novel, low-cost and partially independent of human expertise, AI-based screening tools may be more cost-effective than current visual assessment methods; and highly appealing in low-resource settings with limited health care infrastructure and personnel [127].

'Cases' and 'controls' definition

In cervical screening, 'cases' will correspond to women with a premalignant lesion which has the ability to become an invasive lesion, if left untreated; while 'controls' will correspond to women without precancer, although this may harbor multiple appearances, due to other diseases, artifacts or normal variants.

Each test should determine what defines a 'case' and a 'control' for their algorithm, and different definitions can be used, based on histopathology, HPV testing, visual assessment or the combination of different methods. For example, for one test the ground truth for 'cases' can be the histological confirmation of CIN2+ and for other, it can be the histological confirmation of CIN3+ or [CIN2 and hrHPV(+)]. During the classification analysis, there is likely to be some women falling on the borderline between 'cases' and 'controls'. To avoid misclassification, some tests may formally define an 'intermediate' category (a three-state algorithm), ensuring additional evaluation for these women [129, 130].

The performance of tests with different definitions of what is a 'case' and what is a 'control' will be different, and algorithms that choose sub-optimal and imprecise ground-truth definitions should be avoided.

Training and internal validation

During the training phase, the test will capture multiple features from a diverse set of images, to create patterns. This process is continuously improved through iterations, until the algorithm is capable of labelling each situation, according to their definitions of 'case', 'control' and 'intermediate' (if exists).

The quality of the data set (number and quality of images, variability of cases, representativity of special groups of interest, such as women living with HIV, and inclusion of multiple confounding factors) will interfere with the performance of the algorithm.

The internal validation will assess the repeatability, accuracy and predictive values (risk stratification capacity) of the test, and if unsuccessful, it means the model should be retrained. It uses generally data sets with similar distributional characteristics to the training data (e.g., same device, same geography, same population) thus this validation is not enough to guarantee the generalizability or portability to different settings or populations [127, 129-131].

External validation

External validation will assess the same parameters of repeatability, accuracy and predictive values, but within different settings and with external datasets.

This validation step intends to ensure the recognition of random images, with different features, captured under different conditions (i.e., light), by different operators and in different populations. This capability of being 'device-agnostic' has proven to be hard to achieve and implies retraining of the algorithm to the new device [132]. Retraining and re-assessment may also be needed if other major conditions are changed, and ultimately, new external validation process should be considered before moving to a new setting [130].

Other considerations

Several VIA-related considerations will also apply to AI-based AVE tools, such as the need of having trained health care worker performing a pelvic examination with a speculum. The performance of this method will also be affected by the quality of the acetic acid, the timing of when the images are captured after the acid application or even the anatomic variants of women's pelvis that may make difficult a correct visualization of the cervix.

6.3.3 Analysis of enhanced visual assessment and opto-electrical tools landscape

In this horizon scan, there are five products that have AI-based algorithms embedded to enhance the performance of a visual method, and two digital colposcopes without AI-based algorithms. Their characteristics and stage of development/validation are diverse and direct comparisons may be misleading. Technology Table 6 outlines some of the AI algorithm features (if applicable), and the main hardware characteristics and requirements to operate. Technology Table 7 complements the previous information, with some details only related to digital colposcopy imaging.

Data set size for training and internal validation is provided on Technology Table 6, and all tests included women living with HIV in their training process, except EVA PRO (Mobile ODT, LTD), which doesn't include this group within its target population.

By the time of this review, most developers reported having a two-state algorithm. Only IRIS with AVE algorithm (Liger Medial Inc and PAVE consortium) and the Smart Scope (Periwinkle tech) reported having a three-state algorithm, with an intermediate category. According to the information

provided by the manufacturer, the AVE algorithm for use on IRIS is under external validation in multiple LMIC countries, involving more than 100,000 women, following which the AVE algorithm will be integrated with the IRIS device for an effectiveness study. Smart Scope was externally validated in India, with around 1,600 women included.

AVE (GHLabs/NCI) reported having a two-state algorithm with internal validation published recently [133], and an external validation was conducted across five LMICs, with more than 25,000 women included. Pre-publication data from the external validation study shared at national dissemination events in late 2023 and early 2024 demonstrated AVE's superior sensitivity to VIA. As of this writing, study results are pending publication and expected by end-2024.

SEVIA (SkyConnect Inc.) uses a two-state algorithm for the initial classification of 'VIA positive' and 'VIA negative', and then a three-state algorithm to further classify the positive cases in 'suspicious of cancer', 'VIA positive small lesion' and 'VIA positive large lesion'. This product is under external validation mainly in Tanzania, with 10,000 women planned to be tested.

Pocket Colposcope (Calla Health Foundation) and Gynocular (Gynius Plus AB) only have the functionality of enhancing colposcopy evaluation, through digital imaging, and don't have at this stage any AI-based algorithm included. Only IRIS (Liger Medial Inc) can be used for precancer treatment, as it is also a thermocoagulator (see Technology Table 7 – Digital colposcopy - imaging specific features).

Another product to be mentioned, although it is not a visual assessment tool, is TruScreen Ultra (TruSreen Group Limited), an opto-electrical device, with an AI-based algorithm embedded. This technology uses a single use sensor to interface with the cervix, enabling the assessment of different features of the cells, including electrical properties. Then, through its two-state algorithm, the test is classified as normal or abnormal. According to the information provided by the manufacturer, the algorithm was trained and validated in over 40,000 women, in multiple settings, including some LMIC countries, most significantly in China.

Technology table 6

Enhanced visual assessment tools, including digital imaging and AI-based solutions (Horizon scan – not recommended in the WHO 2021 guidelines)

Horizon scan: enhanced visual assessment tools (AI- and digital imaging-based) (includes technologies that uses AI-based images processing or other characteristics of the cervix tissue)																
					Ground truth									Infrastructure, hardware requirements and interoperability		
Manufacturer	**Product name**	**Allows colposcopy through digital imaging tools**	**Algorithm architecture** (two state / three state) (1)	**Output metric produced**	**Case (positive) definition**	**Control (negative) definition**	**Indeterminate definition or other categories** (if used)	**Countries involved in training and internal validation**	**Which device informed the training and validation algorithm?**	**Training data set size (number of images and women)**	**Internal validation data set size** (number of images and women)	**External validation Location and data set size** (2)		**Ability to work without running power and ability to work offline**	**Software compatible with multiple hardware devices**	**Integration with other health care databases, multiple APIS**
AI-based interpretation																
GH Labs	AVE	✗	Two state	Positive/negative (probability score available on demand)	Histopathology CIN2+	Histopathology <CIN2	N/A	Zambia, Rwanda, Senegal, Malawi, Zimbabwe and India	Samsung A21s as primary device and Samsung J8 used in training additional models	✓ 8,000 images (2,000 women)	✓ (1,362 women)	✓ In progress 5 countries: (25,000 women)		✓	✗	✗
Liger Medical Inc for image capture device and PAVE consortium for the AI-based AVE	IRIS thermocoagulation and digital colposcopy device with AVE algorithm (3)	✓	Three state	Normal / Indeterminate / Precancer. (When combined with HPV extended genotyping, will provide risk stratification in 12 classes)	Histopathology CIN3+/AIS, Histopathologic CIN2 with HRHPV +ve	Histopathology <CIN2 or no histopathology with i) HRHPV -ve ASCUS or ii) HRHPV -ve NILM (if cytology is available), Histopathologic <CIN2 or no histopathology with i) HRHPV +ve and no equivocal cervical changes (if cytology not available) or ii) HRHPV -ve	Histopathology CIN2 with HRHPV -ve, Histopathologic <CIN2 or no histopathology with i) LSIL+ cytology or ii) HRHPV +ve ASCUS or iii) HRHPV +ve NILM (if cytology is available), Histopathology <CIN2 or no histopathology with HRHPV +ve and some equivocal cervical changes (if cytology not available)	Costa Rica, USA, Netherlands	Cerviscope, DSLR camera attached to Zeiss colposcope	✓ 5,669 images (3,300 women)	✓ 1,686 images (938 women)	✓ In progress 1. Zambia: 998 women 2. Bolivia, Brazil, Cameroon, El Salvador, Kenya, Thailand: 644 images from 230 women 3. Brazil, El Salvador , Honduras, Cambodia, DR, Malawi, Tanzania, Eswatini, Nigeria: ~100,000 women		✓	✓ (Android based)	✓
MobileODT, LTD	EVA PRO	✓	Two state	Probability score	Histopathology CIN2+	Histopathology <CIN2	N/A	Poland, India, Ghana	EVA PRO device	✓ (4,000 women)	No data provided	✗		✓	✗	✗
Periwinkle tech	Smart Scope® CX	✓	Three state	Color coded risk stratification: Red, Green, other	Histopathology for positive cases (Swede score >=4)	Normal colposcopy or benign conditions per Smart scope test	Swede score <4 on colposcopy but normal on Smart scope test OR in between cases (not RED or equivalent score and not GREEN or normal)	India, Malawi	Smart Scope® CX	✓ 126,000 images (7,420 women)	✓ 84,000 images (4,640 women)	✓ India: 28800 images (1,600 women)		✓	✗	✓

Horizon scan: enhanced visual assessment tools (AI- and digital imaging-based)
(includes technologies that uses AI-based images processing or other characteristics of the cervix tissue)

Manufacturer	Product name	Allows colposcopy through digital imaging tools	Algorithm architecture (two state / three state) (1)	Output metric produced	Ground truth			Countries involved in training and internal validation	Which device informed the training and validation algorithm?	Training data set size (number of images and women)	Internal validation data set size (number of images and women)	External validation Location and data set size (2)	Infrastructure, hardware requirements and interoperability		
					Case (positive) definition	Control (negative) definition	Indeterminate definition or other categories (if used)						Ability to work without running power and ability to work offline	Software compatible with multiple hardware devices	Integration with other health care databases, multiple APIS
SkyConnect Inc.	SEVIA	✓	Two and three state	Positive/Negative (probability score), and then positive cases are further classified in Suspicious for Cancer / VIA Positive Small Lesion / VIA Positive Large Lesion	Not specified	Not specified	N/A	11 African countries – majority of data coming from Tanzania	Samsung J5, Samsung J8, Samsung A12, Samsung A20 and Samsung A15	✓ 95,000 images (45,000 women)	✓ 45,000 images (15,000 women)	✓ In progress Tanzania: 30,000 images (10,000 women)	✓	✓ (Android and iOS based)	✓
Improved visualization only (no AI-based intervention)															
Calla Health Foundation	Pocket Colposcope	✓	N/A (No AI-based algorithm available) (4)					United States, Honduras, Peru, Tanzania, Zambia and India.	N/A (No AI-based algorithm available) (4)				✓	✓ (Android based)	✗
Gynius Plus AB	Gynocular	✓	N/A (No AI-based algorithm available)					No data provided	N/A (No AI-based algorithm available)				✓	✓ (Both Android and IOS)	✓

Additional information:
(1) Two state: positive/negative; Three state: positive/indeterminate/negative
(2) Unless stated, it will be assumed no independent validation has been conducted
(3) Allows precancer treatment through thermal ablation. See also Technology Table 8 - Devices for treatment of precancerous lesions (includes horizon scan products))
(4) AI-based algorithm in development
AI – artificial intelligence; APIS - Application Programming Interfaces; N/A – Not applicable.
Note: Products are displayed in alphabetical order from manufacturer name. This Landscape reflects primarily information provided by manufacturers/suppliers, at a certain point in time, complemented by literature reviews and expert consultations.

Technology table 7

Digital colposcopy – imaging specific features

Horizon scan: digital colposcopes – imaging specific features					
Manufacturer	**Product name**	**Max optical zoom**	**Max digital zoom**	**Resolution**	**Illumination of the cervix – LED with red-free filter (1)**
Calla Health Foundation	Pocket Colposcope	7.5x	none	5 MP (2)	✓
Gynius Plus AB	Gynocular	12x	Up to 10x (depend on the smartphone used)	48 MP (2)	✓
Liger Medical Inc for image capture device and PAVE consortium for the AI-based AVE	IRIS thermocoagulation and digital colposcopy device with AVE algorithm (3)	3x	4x	Highest: 15.75 line-pairs/mm	✓
MobileODT, LTD	EVA PRO	4x	4x	Highest: 11.78 line-pairs/mm	✓
Periwinkle tech	Smart Scope® CX	No data provided	4x	No data provided	✓

Additional information:
(1) Red-free filter, such as a green filter, highlights blood vessels, improving vascular visualization
(2) Information only available regarding pixel count. Resolution will also depend on the size of the sensor of the camera.
(3) See also Technology Table 8: Devices for treatment of precancerous lesions (includes horizon scan products)
LED - light emitting diode; MP – megapixel.
Note: Products are displayed in alphabetical order from manufacturer name. This Landscape reflects primarily information provided by manufacturers/suppliers, at a certain point in time, complemented by literature reviews and expert consultations.

7.

Treatment of precancerous lesions

Secondary prevention requires cervical cancer screening and should be followed – after triage and/ or confirmation – by appropriate and timely treatment of precancerous lesions and by referral for diagnosis and treatment of lesions that cannot be treated on-site. Treatment should be minimally invasive, safe and effective, and an increase in capacity for treatment is critical, as screening without access to treatment is unethical [3]. Considerations regarding treatment modalities should include the cost of equipment and supplies, the need for electricity or anesthesia, ease of use, the durability of equipment and the ability to scale up in different provider cadres [134].

The basic principle of ablative treatment is to remove the epithelial transformation zone, including the lesion, generally through an outpatient method. If treatment of precancer is needed and eligibility criteria are met, ablative treatment is recommended, including; cryotherapy, laser, thermal ablation (cold coagulation) and diathermy, which apply extreme temperatures to cervical lesions to induce epithelial and stromal destruction of the lesion [135]. All treatments are equally safe and effective and can be performed in an outpatient clinic [15].

In the case of non-eligibility for ablative treatment, because the transformation zone is not visible, the lesion cannot be fully viewed or is too large, or where there is suspicion of cervical cancer, women should be referred for evaluation via colposcopy and biopsies. Excisional treatments (via Large Loop Excision of the Transformation Zone (LLETZ), also commonly known as LEEP) can be offered where extended lesions or cervical precancers exist, and, in the case of cancer, an individual treatment plan should be devised specific to the stage of disease, patient's medical condition and availability of health system resources. It should be noted that, unlike excisional techniques, ablative methods do not allow for histopathological confirmation of disease, the gold standard for diagnosis and may leave room for overtreatment.

Some surgical technologies may be expensive and unsuitable for health providers in low-resource areas. The WHO's cervical cancer elimination strategy highlighted that globally, initiatives need to prioritize to secure affordable, high-quality diagnostics and supplies [3].

7.1 Cryotherapy

Cryotherapy is a WHO-recommended ablative treatment that destroys precancerous areas on the cervix by freezing the abnormal tissue using a supercooled metal disc (cryoprobe) [2]. One major challenge and disadvantage is the freezing process, as it requires a tank with compressed carbon dioxide or nitrous oxide gas, presenting challenges in many LMICs due to the high cost and infrastructure required for transport and maintenance [135]. New cryotherapy technologies are more easily transportable, have less reliance on infrastructure for electricity or gas and have a high level of usability, appropriate for low-level health care providers [134, 136, 137]. These portable treatment tools have been found to be comparable to other cryotherapy devices in terms of the ability to freeze the cervix appropriately and offer an effective treatment modality for outreach testing models or a single-visit screen-and-treat approach.

7.2 Thermal ablation

Thermal ablation (TA), also called 'cold coagulation' or thermocoagulation, is a WHO-recommended ablative treatment method increasingly being adopted as an alternative to cryotherapy [2]. While cryotherapy employs gas to effect controlled freezing of cells, thermal ablation uses a heated probe to destroy cells and tissue on the surface of the cervix, typically at temperatures 100-120 °C [135].

WHO 2019 guidelines for the use of thermal ablation for cervical precancer lesions endorsed the use of TA devices for the treatment of precancerous lesions eligible for ablation, taking into consideration that TA devices show equivalent clinical outcomes to cryotherapy (with minimal adverse impacts, including on fertility) and can help LMICs overcome supply chain and access barriers faced with cryotherapy [135].

Investment in TA allows for decentralization, enabling an increase in overall screening and treatment demand and coverage [138, 139]. New, portable TA devices, relying on solar or battery power, are considerably easier to use and manage than traditional cryotherapy machines as they do not rely on gas. Portable devices can be used at the POC by a variety of health care personnel, and adapted to low-resource settings without stable electricity [135].

WHO 2021 guidelines highlight the advantages of thermal ablation as an alternative to cryotherapy, and with continued demonstrated success in LMICs, it is well-positioned to become the new gold standard for treating patients with precancerous lesions [2, 135].

Case study 4

Multicountry Unitaid-supported project using thermal ablation devices

In response to the WHO's call for the elimination of cervical cancer, in July 2019, CHAI, with funding from Unitaid, launched a multicountry project to increase access to screening and treatment for cervical precancers. Thermal ablation (TA) devices were rolled out with accompanying training and support in partnership with the governments of India, Kenya, Malawi, Nigeria, Rwanda, Senegal, Uganda, Zambia and Zimbabwe to increase access to precancer treatment. Unitaid is also funding related interventions under the SUCCESS project described earlier, in partnership with Jhpiego and UICC, which have introduced TA in Burkina Faso, Cote d'Ivoire, Guatemala and the Philippines [140]. Between 2019 and 2023, Unitaid's investment helped procure and deploy over 6,000 devices across 26 countries.

To help expand the use of portable TA devices, CHAI and Unitaid negotiated global price agreements with Liger Medical LLC (Liger) and Wisap Medical Technologies GmbH (WISAP), which are now offering prices at least 38% and 42% lower than current market prices, respectively.

CHAI further helps to promote clinical skill attainment through basic implementation initiatives that incorporate TA into clinical practice guidelines and assist in initial and ongoing public health system training and mentoring programs. While significant implementation, device management and deployment considerations were required, countries have begun successfully introducing TA devices in the field. The experience using TA devices has been overwhelmingly positive, with several benefits to the use of TA, including ease of use, ease of clinical deployment, improved access, improved health equity, ease of procurement and cost [140]. These benefits have enabled task shifting to a wider cadre of health care workers including nurses now able to deliver treatment services.

The introduction of the TA program has significantly improved access to treatment of precancerous lesions as an immediate, fast, safe and effective treatment that reduces loss to follow-up and increases treatment coverage. TA allows for decentralization of precancerous cervical lesion treatment to more health care facilities due to ease of use, portability and minimal infrastructure needs, with ~50% of the deployed devices across ten programs countries placed at primary health care levels. TA's portability further supports mobile treatment for women unable to visit central health facilities, and possible same-day screening and treatment sessions in camp settings and other community-level health service platforms. This ultimately improves health equity by providing under-screened and untreated women in hard-to-reach areas with additional facilities, as well as mobile clinics, offering necessary care. Previously, women could only receive cryotherapy at a limited number of more centralized facilities that had the necessary infrastructure [140].

Finally, TA procurement is found to be easier than that of cryotherapy, as TA requires only coordination with the dedicated supplier at a standardized price, while for, cryotherapy, logistics should be managed with device manufacturers and different suppliers to secure gas cylinders and regular gas supply, consumables susceptible to price fluctuations [140].

7.3 Large loop excision of the transformation zone (LLETZ)

LLETZ, also called LEEP (loop electrosurgical excision procedure), uses a wire loop heated by electric current to remove cells and tissue on the surface of the cervix. LLETZ/LEEP serves a dual purpose to remove the lesion and extract a specimen for pathological examination. The procedure can be performed under local anesthesia on an outpatient basis and usually takes less than 30 minutes but should only be performed by a highly trained health-care provider because of the risk of adverse events, including hemorrhage. LLETZ is preferred in situations in which the lesion is considered too large to be adequately removed through ablative therapies or in the situation in which multiple ablation attempts have failed to successfully remove the lesion.

As an excisional treatment, it is technically more complex, requires more specialized human resources and should be performed in a facility with the conditions to manage some possible complications, such as severe bleeding related to the procedure. These specificities may constitute important constraints for the broader implementation and access to this treatment technique within LMIC settings.

7.4 Treatment devices for precancerous cervical lesions landscape

The landscape for precancer treatment devices has been evolving, mainly for thermal ablation, considering its importance and impact in precancer treatment in the LMIC context. Technology Table 8 summarizes the precancer treatment products included in this landscape, as well as two devices in the late stage of development (horizon scan). To be considered for inclusion in the landscape, manufacturers had to reply to an open RFI (see section 2. Summary of Methods). Only one LLETZ/LEEP device and no cryotherapy device manufacturers responded to the RFI. It should be noted, therefore, that this report should not be considered a comprehensive survey of the existing market for these technologies across all low- and high-income countries.

Technology table 8

Devices for treatment of precancerous lesions (includes horizon scan products)

Precancer treatment devices								
			Operational requirements and functionalities					
Manufacturer	Product name	Minimum number of probes included in the kit	Ability to work without running power supply	Time to complete charge	Number of treatments between charges	Probes lifetime (1)	Safety features – e.g. heat protection	Warranty
Thermal ablation								
Liger Medical LLC / MobileODT, LTD by Liger Medical	Thermocoagulator HTU-110 / Thermoglide	4	✓	2 h	30	120 cycles	✓	2 year
WISAP Medical Technology GmbH	C3 ECO4	4	✓	No data provided	100	150 cycles	✗	1 year-device 6 months-batteries
WISAP Medical Technology GmbH	C3 Mobile Thermal Ablation Device	2	✓	No data provided	100	250 cycles	✓	1 year
WISAP Medical Technology GmbH	Cold Coagulator 6001	0	✗	NA	N/A	Several hundred (300+)	No data provided	1 year
LLETZ/LEEP (2)								
Liger Medical LLC	Electrosurgical Unit ESU-110 LEEP	N/A	✓	6 h	5	N/A	✓	2 year
Horizon scan								
Deepak care Zepnur Private Limited	Thermal Ablation Device	No data provided	✓	No data provided	15	No data provided		1 year
Liger Medical LLC (3)	IRIS thermocoagulation and digital colposcopy device with AVE algorithm	4	✓	No data provided	No data provided	300 cycles	No data provided	No data provided

Additional information:
All thermal devices presented can be operated by trained nurses or midwives.
For all devices, time to perform treatment depends on user and type of lesion, running from seconds to few minutes.
(1) Probe lifetime may vary with disinfection process - recommended to follow IFU (instruction for use)
(2) There are more LLETZ/LEEP available on the market. To be considered for inclusion in the landscape, manufacturers had to reply to an open RFI (see section 2. Summary of Methods). This is provided here as a comparable example in relation to characteristics of thermal ablation devices.
(3) See also Technology Table 6 - Enhanced visual assessment tools, including digital imaging and AI-based solutions (Horizon scan – not recommended in the WHO 2021 guidelines) and Technology Table 6 – Digital colposcopy - imaging specific features

HCW - health care worker; LLETZ - large loop excision of the transformation zone; LEEP - loop electrosurgical excision procedure; N/A – not applicable; RFI – request for information
Note: Products are displayed in alphabetical order from manufacturer name. This Landscape reflects primarily information provided by manufacturers/suppliers, at a certain point in time, complemented by literature reviews and expert consultations

7.4.1 Analysis of the treatment devices landscape

Four different thermal ablation devices are on the market, from two manufacturers: WISAP Medical Technology GmbH and Liger Medical LLC, which acquired MobileODT, LTD, in 2022.

The Cold Coagulator 6001 (WISAP) (Figure 17-B) has multiple other indications, beyond treatment of cervical precancerous lesions. Although considered a versatile device, it needs a running power supply to operate, is considered less portable and does not come with any type of probes. All other products can work with batteries, which is particularly important in an outreach setting.

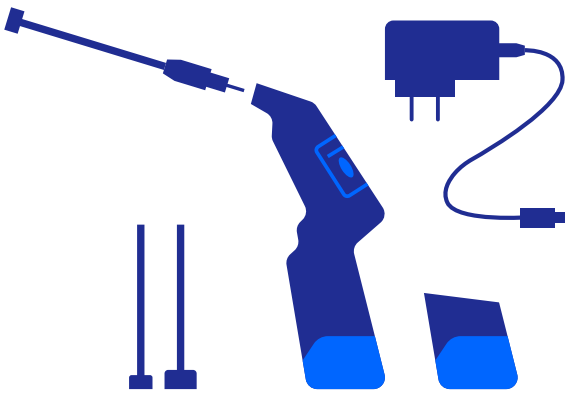
The two C3 thermocoagulators from WISAP (C3 Mobile Thermal Ablation Device and C3 ECO4) are very similar in terms of functionalities and, as battery-powered, are considered portable. However, they differ in terms of the material used for the probes, which may justify the difference between their expected lifetimes and the C3 ECO4 does not have a slider for heat protection. Liger similarly offers two thermal ablation devices (Thermocoagulator HTU-110 and Thermoglide under MobileODT), with similar features with except for variations in probe lifetime.

Beyond the thermocoagulator devices, Liger Medical LLC also provided information regarding a LEEP/LLETZ device, the Electrosurgical Unit ESU-110 LEEP and a pipeline product, the IRIS device, which can be used for colposcopy, supported by an inbuilt AI-based AVE algorithm, and thermal ablation.

Figure 17

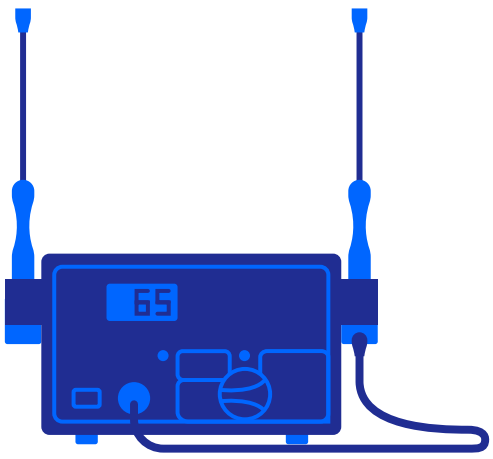
A

Generic representation of portable thermal ablation devices similar to C3 Mobile Thermal Ablation Device (WISAP); C3 ECO4 (WISAP); Thermocoagulator HTU-110 (Liger Medical) and Thermoglide (MobileODT, by Liger Medical).



B

Representation of Cold Coagulator 6001 (WISAP).



Source: WISAP website.

7.4.2 Cost considerations for treatment devices

Any pricing comparisons should be made between devices within the same category, as it is not possible to compare thermal ablation devices with cryotherapy or with other treatment modalities, such as LEEP. This section only provides considerations regarding thermal ablation devices.

Thermal ablation is considered to be low-cost, accessible to low-resource settings and appropriate for low- to mid-level providers due to its ease of use [135, 138]. The affordability of TA devices has arisen as a result of extensive global price negotiations by Unitaid and CHAI with two key manufacturers, which significantly reduced prices of TA devices (by up to 50%) [135, 141]. Negotiated prices are accessible for all LMICs (as per World Bank classification) under procurement with UNICEF Supply Division, or direct from supplier for specified eligible LMICs [135]. Since procurement options vary in price, incoterms and length of validity, please see the Unitaid-CHAI Fact Sheet on portable thermal ablation device global price agreements [135]. Unitaid-CHAI-manufacturer negotiations are ongoing to ensure longevity of agreements with current devices, and price reductions for newly developed devices.

Main considerations for thermal ablation device procurement that may impact pricing are:

- Kit configuration, including number and type of probes provided;
- Minimum quantity to order (if any);
- Incoterms – similarly to what was described previously for HPV testing platforms, similar incoterms don't mean all the supply chain costs are exactly the same;
- Maintenance accessibility, specific conditions and charges;
- Warranty and expected lifetime of different components, including probes.

Conclusion

Cervical cancer is one of the most preventable and treatable forms of cancer as long as it is detected early and managed effectively. Secondary prevention enables early detection and treatment of precancerous lesions of the cervix. When diagnosed at a precancerous stage, treatment can be provided as an effective outpatient intervention, reducing unnecessary morbidity and mortality associated with more advanced stages of cancer. For secondary prevention strategies to be effective, clinically validated high-performance HPV screening tests, triage tests and treatment procedures should be widely available and implemented effectively at the programmatic level.

The substantial health disparities for cervical cancer observed in LMICs reflect access barriers and disparities in the delivery of screening and other prevention services. These barriers should be addressed as a global effort to help set each country firmly on the path toward cervical cancer elimination.

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