CERVICAL CANCER

SCREENING AND TREATMENT OF PRE-CANCEROUS LESIONS FOR SECONDARY PREVENTION OF CERVICAL CANCER

TECHNOLOGY LANDSCAPE

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ABBREVIATIONS AND ACRONYMS

AI	Artificial Intelligence
CE-IVD	Conformité Européenne, in vitro diagnostics
CIN	Cervical Intraepithelial Neoplasia
CxCa	Cervical Cancer
DNA	Deoxyribonucleic Acid
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
IARC	International Agency for Research on Cancer
LBC	Liquid-Based Cytology
LLETZ	Large Loop Excision of the Transformation Zone
LFA	Lateral Flow Assay
LMICs	Low- and Middle Income Countries
NCI	National Cancer Institute
NGO	Non-Governmental Organization
PCR	Polymerase Chain Reaction
POC	Point of Care
RNA	Ribonucleic Acid
RUO	Research Use Only
TB	Tuberculosis
VIA	Visual Inspection with Acetic Acid
WHO	World Health Organization

EXECUTIVE SUMMARY

In support of the WHO 2030 goal toward the elimination of cervical cancer as a public health problem, Unitaid seeks to accelerate access and scale use of optimal tools for cervical cancer secondary prevention in low- and middle-income countries. The objective of this landscape is to provide an overview of technologies for secondary prevention of cervical cancer, particularly for screening, diagnosis, and treatment at the critical stage of intervention for pre-cancerous lesions. This landscape identifies some of the critical technology and access barriers for managing the disease at the pre-cancer stage, as well as points toward opportunities to reduce the impact of cervical cancer in low and middle-income countries (LMICs).

Strategies that identify women at risk of cervical cancer and provide them early detection and treatment at the pre-cancer stage have dramatically decreased incidence and mortality of cervical cancer in several high-income countries. There is an urgent need for a paradigm shift in screening for cervical cancer in many LMICs in order to achieve broader impact through equitable access to early detection and treatment of pre-cancer. Women living with HIV are particularly vulnerable, with HPV co-infection progressing more frequently and rapidly to cervical cancer. Even as countries introduce the HPV vaccine, access to efficient screen-and-treat programmes will remain key for several decades to reach unvaccinated vulnerable women and to identify cases in the vaccinated cohorts.

A number of technologies are available on the market that are recommended as cost-effective and may therefore be considered in priority interventions for LMICs. However, tools, such as HPV molecular tests and alternative treatment devices, are out of reach for most populations in need, with access barriers on both the supply and demand sides of the markets for these technologies. Such barriers mean that healthcare workers in LMICs rely on the use of substandard tools and strategies for management of pre-cancer and prevention of cervical cancer and cervical cancer-related mortality. In addition, market shaping is needed to improve the affordability and availability of high-quality screen-and-treat tests and other medical devices. Promising new screening technologies need a pathway for development along with a process for national regulatory approval across regions, with an effective deployment strategy in combination with market-shaping interventions to increase availability and affordability.

Unitaid supports the advancement of innovative cervical cancer screening and treatment tools to enable a paradigm shift in screening and treatment programmes in LMICs, by 1) catalyzing markets for cervical cancer screening and treatment by addressing access barriers for the most promising new technologies; and 2) supporting introduction of these products in selected early-adopter countries through effective delivery channels.

BACKGROUND

Cervical cancer is the fourth most common cancer among women globally, with 570,000 new cases and 311,000 deaths (7.5% of all female cancer deaths) in 2018.[1,2] It is one of the leading causes of cancer deaths among women in LMICs, as more than 85% of deaths occur in less developed regions where the disease distribution coincides strongly with HIV infection. Cervical cancer is one of the most preventable and curable forms of cancer, as long as it is detected early and managed effectively.

Virtually all cervical cancers are caused by infection with human papilloma virus (HPV), the most common sexually transmitted infection (STI). There are more than 100 types of HPV with at least 13 high-risk types linked to cancer. The highest-risk types 16 and 18 together are responsible for approximately 70% of cervical cancer cases globally. Although most HPV infections clear up on their own, and most pre-cancerous lesions resolve spontaneously, chronic HPV infection can progress to invasive cervical cancer if undetected and untreated.

Cervical cancer occurs 4 to 5 times more frequently in immunocompromised women, such as those with untreated HIV infection. While cervical cancer can take 15-20 years to develop in women with normal immune systems, it can progress within 5-10 years in women with weakened immune systems. HIV-HPV co-infected women have been found to develop cervical cancer at ages up to 15 years younger than HIV-negative patients.[3] Rates are compounded by lack of access to life-saving treatment in settings where the burden and need is highest. Among women living with HIV, HPV prevalence rates are higher than in the general population, reaching levels as high as 80% in Zambia and 90–100% in Uganda.[4,5] Once infected with HPV, women with HIV are more likely to develop pre-invasive lesions that quickly progress into invasive, life-threatening cervical cancer.

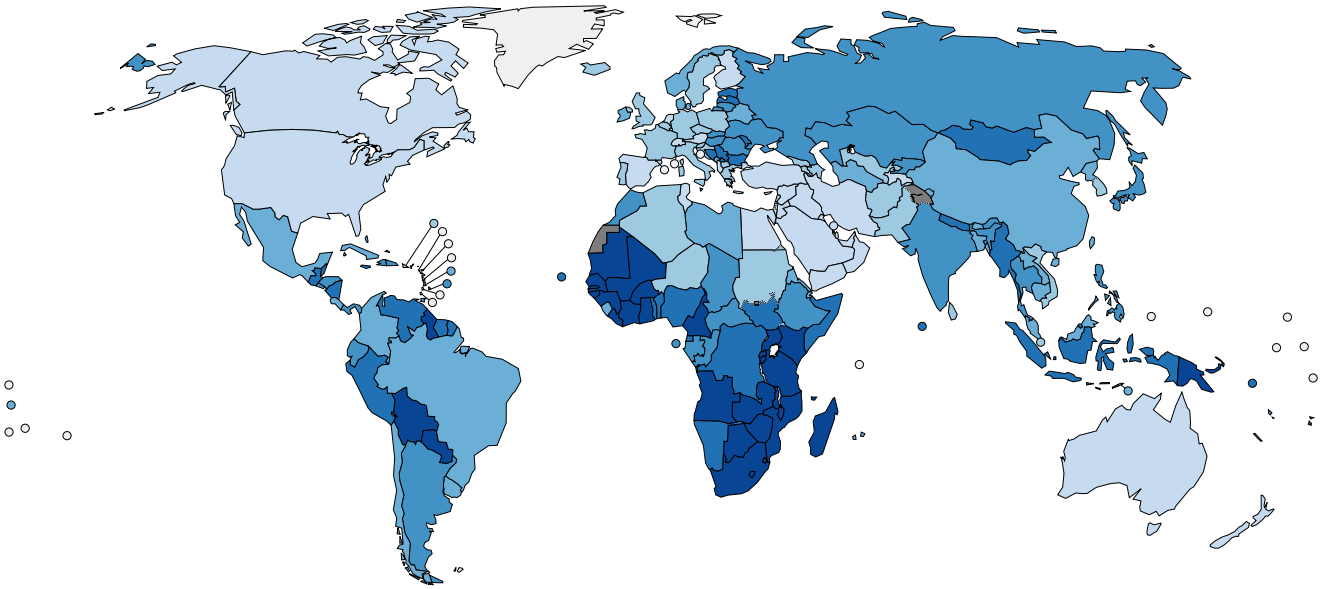
The WHO global strategy towards the elimination of cervical cancer as a public health problem[6] calls for a comprehensive, population-based approach to put all countries on the path to the elimination of cervical cancer within the century. It covers the period 2020-2030. The strategy proposes an approach that will enable countries to reach the 2030 global targets for key interventions that, in turn, will lead to elimination of cervical cancer as a public health problem (hereafter referred to as “elimination”). The proposed targets for 2030 are:

- **90%** of girls fully vaccinated with the HPV vaccine by 15 years of age;
- **70%** of women are screened with a high-precision test[a] at 35 and 45 years of age; and
- **90%** of women identified with cervical disease receive treatment and care.

To achieve elimination in the shortest period of time and with maximum impact, focused action across the continuum of care is required, including increased coverage of HPV vaccination, increased coverage of screening and treatment of pre-cancer lesions, and increased diagnosis and treatment of invasive cancer in an early phase, as well as palliative care.

a A WHO recommended high-precision test with performance characteristics similar to or better than a HPV test.

FIGURE I Age standardized (World) incidence rates, cervix uteri, all ages



ASR (World) per 100 000

≥ 28.4 | 20.2 – 28.4 | 14.7 – 20.2 | 10.3 – 14.7 | 6.5 – 10.3 | < 6.5

Not applicable | No data

Source: http://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf

INTERVENTIONS FOR CERVICAL CANCER

Strategies that identify women at risk of cervical cancer and provide them early detection and treatment at the pre-cancer stage have dramatically decreased incidence and mortality of cervical cancer in high-income countries. While primary interventions focus on prevention of disease, secondary intervention strategies involve screening, detection and treatment of disease at a preclinical stage to prevent the development of cervical cancer. In particular, screening is an important secondary prevention strategy to detect disease at an early and asymptomatic stage when treatment is highly effective.[7,8,9,10] Access to efficient screen-and-treat programs is critical to reducing mortality due to cervical cancer, particularly in low-resource settings with little capacity for tertiary (surgical) interventions for advanced cervical cancer. Along with primary prevention such as HPV vaccination,[11] secondary prevention is needed to achieve reduced mortality in the near term and to move more quickly toward the 2030 WHO elimination targets.

FIGURE 2 Prevention strategies for cervical cancer, with a focus on secondary prevention

Primary prevention: Vaccination and awareness

- HPV vaccination for 9-14 year olds
- Sexuality education
- Condom promotion/ provision
- Male circumcision

Secondary prevention: Screening and treatment

- Screening with HPV and/ or VIA
- On-site treatment for eligible lesions
- Referral for LEEP for larger lesions
- Referral for diagnosis of suspected cancer

Tertiary prevention: Cancer treatment and care

- Surgery
- Radiotherapy
- Chemotherapy
- Palliative care

There is an urgent need to achieve broader impact and equitable access for secondary prevention in LMICs. Approximately 85% of incident cervical cancers and 87% of deaths resulting from cervical cancer occur in LMICs, but only 5% of women are screened for HPV.[12] Current screening and treatment tools available in resource-limited settings are affected by severe constraints, including low sensitivity and efficacy; lack of linkage to care following diagnosis and loss to follow-up; logistics constraints and lack of adequate human resources to effectively deploy these tools at scale.

A number of technologies for secondary prevention are available and cost-effective and are therefore priority interventions for LMICs. Unfortunately, emerging screening tools and treatment devices are out of reach for many populations in need, with severe access barriers on both the supply and demand side. Innovative tools are on the horizon that could address one or more of these challenges and enable accurate and safe screening and treatment of women in the same visit, leading to efficiencies both in terms of resources and public health outcomes (decrease in mortality). In tandem with the HPV vaccine scale-up, the new generation of accessible technologies for secondary prevention make the elimination of cervical cancer possible.

Commercial technologies for secondary prevention of cervical cancer that can be used across a variety of testing environments are presented below, with an emphasis on technologies that can be available for point-of-care settings appropriate for LMICs.

Screening and Diagnosis

While HPV vaccination is an important prevention strategy, cervical cancer screening is critical to women who remain at risk for HPV infection and the development of pre-cancer and cancer. Cervical cancer screening involves detection of pre-cancerous lesions and cancer among women who may otherwise have no symptoms and may feel perfectly healthy. When detected, pre-cancerous lesions can be treated and progression to cancer can be avoided. Cancer that is detected at an early stage has a high potential for cure.

WHO currently recommends three types of screening tests: HPV testing for high-risk HPV types,[13] conventional Pap smear and liquid-based cytology (LBC), and visual inspection with acetic acid (VIA). As pre-cancerous lesions take many years to develop, repeated screening is recommended for every woman above age 30 (frequency depends on the screening test and risk category).[12,14]

HPV Testing

For women living with HIV who are sexually active, HPV testing is recommended every year for HIV-positive girls and women. HPV testing is being incorporated into cervical cancer prevention programmes in high-resource settings as a primary screening test. HPV testing does not necessarily require visualization of the cervix. A health-care provider can collect a sample of cells by inserting a small brush or other appropriate device deep into the vagina, and then placing it in a small container with an appropriate preservative solution; it may also be collected at the time of a speculum examination. See also the self-collection section below.

HPV testing has very high sensitivity, however as infection and pre-cancerous lesions can spontaneously resolve, HPV testing has a lower specificity for cancer than cytology. A negative HPV test almost completely eliminates the risk of development of a precancerous or cancerous lesion (CIN3+) within 5 years. However, a positive HPV test does not confirm pre-cancer; it only confirms that there is an HPV infection.

Molecular HPV (DNA) testing: Molecular HPV testing is based on the detection of HPV DNA from high-risk HPV types in vaginal and/or cervical samples, and most laboratory tests can detect up to 15 HPV types. HPV tests can either detect the high-risk HPV genotypes in bulk without distinguishing the individual types or can detect separate HPV types via some genotyping capacity. It should be noted that the use of molecular testing alone can lead to a substantial proportion of overtreatment when HPV positive women are treated without triage or confirmation of pre-cancer. A screening algorithm may prove useful to avoid overtreatment, possibly including the newer biomarker tests for patient triage as described below. Molecular testing is the preferred test method, per WHO recommendations, however it is expensive and almost exclusively available in centralized laboratories.

TABLE I HPV nucleic acid tests

Product Name	Manufacturer	Test Format	Test format	Regulatory Approvals
Alinity m High Risk (HR) HPV	Abbott	HPV DNA molecular test	High throughput	CE IVD
Aptima HPV	Hologic	HPV RNA molecular test	High throughput	US FDA, CE IVD, TGA, HC
careHPV	Qiagen (CN) in collaboration with CARE Inc. (USA)	HPV DNA molecular test	Medium throughput	CE IVD, WHO PQ
Cervista HPV 16/18 assay	Hologic	HPV DNA molecular test	Medium throughput	FDA, TGA
cobas® 4800/6800/8800 HPV	Roche	HPV DNA molecular test	Medium to very high throughput	FDA, CE IVD, TGA, HC
Digene Hybrid Capture 2 High-Risk HPV DNA test	Qiagen	HPV DNA molecular test	Medium to high throughput	FDA, CE IVD, TGA, HC
Harmonia HPV, Venus HPV kit	Liferiver/Shanghai ZJ Bio-Tech Co. Ltd	HPV DNA molecular test	Medium to high throughput	CE IVD
MeltPro® High Risk HPV Genotyping Assay	QuanDx	HPV DNA molecular test	Medium to high throughput	CE IVD
Onclarity HPV Assay	BD	HPV DNA molecular test	Medium throughput	FDA, CE IVD, TGA, HC, PMDA
RealTime High Risk (HR) HPV	Abbott	HPV DNA molecular test	Medium throughput	CE IVD, TGA, HC, PMDA
Xpert HPV	Cepheid	HPV DNA molecular test	POC to high throughput	CE IVD, WHO PQ, TGA, HC
NUCLISENS® EASYQ® HPV	Biomerieux	HPV DNA molecular test	Medium to high throughput	Discontinued
Ampfire HPV	Atila Biosystems	HPV DNA molecular test	Low to medium throughput	In development
NEDxA	Genomica	HPV DNA molecular test	POC	In development
Q-CAS HPV	QuantuMDx / Global Good	HPV DNA molecular test	POC	In development
Truenat HPV-HR	Molbio	HPV DNA molecular test	POC	In development

Source: communication from manufacturers and manufacturer websites

New point-of-care (POC) HPV tests are coming into the market and are intended for use in LMICs. These HPV tests are intended to be portable and simple to operate, so that they may be performed at clinics and primary care centres rather than at centralized laboratories, by personnel with minimal technical training.[15] Two near POC tests have currently received WHO Prequalification.

Figure 3: Cepheid Xpert

© Cepheid

Xpert HPV (Cepheid, USA)

is a cartridge-based test which is run on the GeneXpert platforms, real-time PCR platforms validated for TB diagnosis, HIV diagnosis, HIV viral load and HCV viral load and others. The test is performed in less than one hour and can be run on any of Cepheid's GeneXpert platforms, all of which require consistent electricity and are operated through a laptop or desktop computer. It detects 14 high risks HPV types among which HPV16 and HPV18/45 are individually typed.[16] The Xpert HPV assay is CE-marked since 2014 and received WHO Prequalification in 2017.[17]

Figure 4: *care*HPV Test

© Qiagen

*care*HPV Test Kit (Qiagen, China in collaboration with CARE Inc, USA)

has been developed by CARE (Cooperative for Assistance and Relief Everywhere, Inc.) for resource-limited settings and is manufactured and marketed by Qiagen GmbH. The test detects 14 high-risk HPV types and requires around 2.5 hours processing time.[18] It requires a skilled laboratory technician, as there are several manual processing steps required for batch processing using 96 well plates. The *care*HPV assay is CE-marked since 2010 and received WHO-prequalification in 2018.[17]

HPV oncogenic biomarkers

Because traditional molecular tests have high sensitivity but cannot distinguish between clinically relevant infections and those that may spontaneously resolve, there is a need for additional triage tests to more accurately identify women with true pre-cancer. Biomarkers have been identified which are indicative of chronic infection and oncogenic activity. HPV-induced malignancy disrupts normal cell cycle regulatory mechanisms, resulting in over-expression of the oncoproteins E6 and E7 which in turn transform the host cell. Oncogenic activity can be shown by detecting HPV RNA transcripts, antibodies raised against HPV antigens (HPV16 L1), or oncoprotein-induced DNA methylation. Elevated levels of these biomarkers can serve as an indicator or risk factor for pre-cancerous and cancerous lesions.

Oncogenic biomarker tests therefore provide greater specificity for high-risk disease progression than the simple yes/no of HPV infection using the nucleic acid tests. In combination with HPV DNA tests, the oncogenic tests could therefore improve diagnostic accuracy compared to what can be achieved by traditional HPV DNA tests. However, though there are several commercially-available HPV biomarker tests, the majority require advanced laboratory infrastructure and are not routinely used; others with improved simplicity are still in development (Table 3). The cost effectiveness and impact of emerging biomarker tests are currently under evaluation.

TABLE 2 HPV biomarker tests

Name	Developer	Biomarker	Test format	Regulatory Approvals
HPV OncoTect® 3Dx™ E6, E7 mRNA	InCellDX	HPV RNA	flow cyotmetry assay	CE-IVD
OncoE6 Oncoprotein Cervical Test	Arbor Vita Coorporation (USA)	Oncoprotein LFA	POC - lateral flow assay	CE-IVD
CerMark™ Cervical Cancer Screen immunoassay	OncoGenesis	Protein biomarker assay	POC or lab immunoassay	In development
Prevo-Check HPV16 L1 immunoassay	Abviris	anti-HPV serological test	POC or lab immunoassay	CE-IVD*
GynTect® methylation PCR assay[ii]	oncgnostics GmbH	methylated DNA	methylation specific PCR	CE-IVD
QIAsure Methylation Test PCR kit	Self-screen B.V. / QIAGEN	methylated DNA	methylation specific PCR	CE-IVD

Source: communication from manufacturers and manufacturer websites

*CE-IVD marked for the detection of HPV16-induced head/neck and anogenital carcinoma

Highlighted below is the most widely available biomarker test that is suited to more decentralized testing in LMIC.

Figure 5: Onco*E6* Cervical Test

© Arbor Vita

Onco*E6* Cervical Test (Arbor Vita, USA)

Is a rapid lateral flow assay, which requires several manual steps, based on the detection of E6 oncoprotein biomarkers[19] with high specificity but low sensitivity. The test kit is available in Europe. WHO in collaboration with the International Agency for Research on cancer (IARC) is planning operational research to evaluate this triage POC test, and its cost effectiveness, in a large cohort of women including women living with HIV.

Self-sampling

The majority of current laboratory-based HPV screening tests rely on cervical-specimen collection by a clinician. However, self-collected samples for HPV testing provide an additional strategy to overcome cultural and logistical barriers toward accessing the health system and reference laboratory or hospital screening programme.

There are many products for self-collection of cervical specimens (see Appendix B), designed as kits comprised of a single-use swab or cervical brush with a tube containing collection/transport medium. A recent meta-analysis found good performance and acceptability of self-collected samples in LMICs.[20] The study data for self-collection indicate similar accuracy rates as clinician specimen collection. Current prices for cervical or vaginal specimen collection devices are relatively high and most HPV molecular assays are only approved for use with clinician collected sample, therefore there is a need for more widely validated sample collection products.

The self-collection process follows similar steps for the majority of products: 1) insert swab/brush into the vagina and gently rotate for 10-30 seconds, 2) remove swab/brush and transfer it into the collection tube, 3) snap off swab/brush shaft and cap the collection tube, 3) discard shaft, and 4) label collection tube and transport sample to laboratory. Once in the collection tube, specimens are stable at room temperature for at least 24 hours and some for more than 30 days. For the most part, the self-collection process is acceptable to women and perceived as discreet, private and time-saving. The process is described by participants as female-friendly, painless and quick.

FIGURE 6 Examples of self-collection devices for HPV testing

Qvintip™, Aprovix AB

© Aprovix, AB

Evalyn Brush, Rover Medical Devices

© Rover Medical Devices

FLOQSwabsTM, Copan Flock Technologies

© Copan Flock Technologies

SelfCerv, Hologic/Ilex

© Hologic/Ilex

Other Screening Methods

Cytology: Cytology-based screening involves taking a sample of cells from the ectocervix and endocervix during a pelvic exam. The Papanicolaou smear (Pap smear) or liquid-based cytology (LBC) are the two used methods. The cells are either fixed on a slide at the facility (Pap smear) or placed in a transport medium (liquid-based cytology) and then sent for laboratory analysis. Depending on national policy, women with abnormal cells are advised further assessment with colposcopy, repeat cytology or HPV detection tests, depending on the cellular pathology.

Cytology screening requires highly-trained technicians and a substantial amount of laboratory equipment and can take several days to weeks for results. While cytology has shown conclusive effectiveness from observational studies in reducing cervical cancer incidence and mortality, it has also suffered from sub-optimal sensitivity and false negative results due to sampling problems or interpretation error, particularly in LMICs where cytology-based programmes are expensive and difficult to implement. However, Pap smear is more specific than HPV testing, so it could be used for triage testing after a positive HPV test result (where available) to avoid overtreatment of cervical lesions.

Visual inspection with acetic acid (VIA): Visual inspection with acetic acid (VIA) is a simple method for detecting early cell changes to the cervix. Lesions on the cervix turn white after application of 3-5% acetic acid (vinegar), with the density and characteristics of the whitening depending on the severity of the lesions. VIA is quite inexpensive, utilizes locally sourced supplies (vinegar and cotton), and does not rely on laboratory services. However, the subjective interpretation of the unaided visual result can have significant variation in accuracy. Service providers need appropriate training as well as ongoing quality control and quality assurance. VIA is the option used in most LMICs, but VIA's success in accurately detecting precancerous lesions remains very low despite the significant levels of investments dedicated to the approach over the years. An alternative visual screening method is visual inspection after application of Lugol's iodine (VILI), which is more sensitive and similarly specific, but requires a product that is not as easily accessible as vinegar.

Enhanced digital analysis: As described above, visual imaging methods of identification of cervical pre-cancer depend upon subjective interpretation of the unaided visual result which has been shown to have substantial variation in accuracy. A number of tools are in development to enhance the accuracy of detection, from aids to enhance visual evaluation to new POC technologies, allowing remote assistance by expert colposcopists. To improve the accuracy of visual inspection, new artificial intelligence (AI) visual inspection algorithms are being developed to detect cervical cancer or pre-cancer within seconds from a single image of the cervix. Automated visual evaluation (AVE) can detect signs of cancer or pre-cancer during a speculum examination with over 90% accuracy; AVE was shown to outperform interpretation of the same images by expert clinicians.[21] AVE is being developed and improved at present by a not-for-profit collaboration of public health scientists, led cooperatively by the National Cancer Institute (NCI) and Intellectual Ventures' Global Good. AVE is expected to provide a much more accurate and cost-effective method of cervical cancer screening than VIA, available as a free-standing application (not requiring internet access) on a common cellphone camera.

TABLE 3 Digital imaging approaches

Name	Developer	Test format	Development stage
Advanced visual evaluation (AVE) app	NCI / Global Good	POC – mobile phone	In development
Gynocular	Gynius AB / Woman Care Global	POC – handheld colposcope, smartphone adaptor	FDA
EVA COLPO	MobileODT	POC – handheld smartphone colposcope	FDA, CE IVD
High Resolution Micro-endoscopy (HRME)	Rice University	Fiberoptic microendoscopy	In development
TruScreen	TruScreen	POC – optoelectronic intraepithelial screening	CFDA
POCkeT colposcope	Duke University	POC – handheld colposcope	FDA 510(k)

Source: communication from manufacturers and manufacturer websites

Colposcopy

Colposcopy is a procedure that provides a magnified and illuminated view of the vulva, vaginal walls, and cervix. Colposcopy is used to visualize the epithelial (surface) layer and underlying blood vessels and is generally performed when the Pap smear or the cervix appearance is abnormal. Colposcopy testing involves acetic acid wash, use of color filters and is used to define the location for taking biopsies and for directing treatment of cervical pre-cancer.

Figure 7: Gynocular
© Gynius AB

Gynocular® (Gynius AB, Sweden)

is a mobile colposcope that has been developed by Woman Care Global, a global non-profit healthcare company, and licensed to the Swedish-based manufacturer Gynius. The Gynocular® is lightweight (480 g) and makes use of cutting edge optics, a green filter, and warm LED lighting. It is equipped with three different levels of magnification and is battery powered with a charge lasting a full day. It can be used in conjunction with a smartphone adaptor that allows clinicians to capture, store, and send high quality digital images of a patient's cervix to others. When connected to a cell phone's video app or to a computer running Skype, it is also possible to send motion picture images.[22] A stand is available to mount the device. The Gynocular® was FDA approved in 2015. Several studies have been published on the use of Gynocular®.[23,24,25,26,27]

Figure 8: EVA System
© MobileODT Ltd.,

EVA COLPO® (MobileODT Ltd., Israel)

an optical imaging device, is a mobile colposcope including a mobile application running on Android phones. It enables remote image capture and patient information tracking. It is linked to an online portal for collaboration and image annotation and reporting, and to enable colposcope-quality imaging. The system is deployed in about 20 countries. It received US FDA approval in December 2016.[28]

Figure 9: HRME
© Rice University

High Resolution Micro-endoscopy / HRME (Rice University, USA)

is a millimeter-wide fiber-optic cable developed by Rice University.[29] This device uses fiberoptics to identify abnormal nuclear activity, a sign of cancer. A study assessing HRME to screening for Cervical Cancer and its precursors in Brazil (HRME-UH2) has been completed in collaboration with the US National Institutes of Health.[30]

Figure 10: TruScreen
© TruScreen

TruScreen (TruScreen, Australia)

uses a pen-like wand to pulse low level electrical and optical signals and examine the cervical tissue. A single-use sensor with precision lens and electrodes is used to interface with the cervix and protect against cross-contamination. The TruScreen hand held device measures backscattered light, direct reflectance and electrical response curves and provides immediate results for appropriate patient care. Unlike cytology, TruScreen does not only examine surface epithelial cells. Light at specific frequencies is transmitted through cervical tissue identifying changes in the basal and stromal layers, including increases in blood circulation and variations in cell nuclei and cytoplasm that occur with pre-cancerous change.

POCkeT Colposcope (Duke University, NC, USA) has a design very similar to a transvaginal ultrasound transducer. It uses a consumer grade digital camera found in the commonly used iPhone 4 and consumer grade LEDs used in standard colposcopes (LeisegangOptik 2). All fit into the form factor of a tampon, a common feminine hygiene product. The proximity of the device to the cervix allows great magnification and pictures. Guided biopsies can be taken with the device in place. It connects to a laptop, tablet or phone for storage and transmission of data. The device has been tried in various countries including Peru, Honduras, USA, India, Kenya, Zambia, Tanzania, Ghana, with Costa Rica trials starting soon.

Treatment of pre-cancerous Lesions

Secondary prevention requires cervical screening and should be followed – after triage and/or confirmation - by treatment of pre-cancerous lesions and by referral for diagnosis and treatment of lesions that cannot be treated on-site. Treatment should be minimally invasive, safe and effective. The basic principle of treatment is to remove the epithelial transformation zone including the lesion, generally through an outpatient method. The majority of pre-cancerous lesions can be treated with ablation, although some will require excision[b]; currently used methods include cryotherapy, thermal ablation and Large Loop Excision of the Transformation Zone (LLETZ).[31] Other surgical technologies may be expensive and unsuitable for health providers in low-resource areas. However, excisional procedures may be preferred in case of extended lesions or suspicion of glandular cervical (pre-) cancer. Cryotherapy is the most common method for treatment of pre-cancerous lesions, as it can be performed without anesthesia at all levels of the health system.

Cryotherapy: Cryotherapy destroys pre-cancerous areas on the cervix by freezing the abnormal tissue using a supercooled metal disc (cryoprobe). This freezing process requires a tank with compressed carbon dioxide or nitrous oxide gas, which can present challenges in LMICs due to the high cost and infrastructure required for transport and maintenance. New cryotechnologies (e.g. CryoPen and CryoPop) are more easily transported and have less reliance on infrastructure for electricity or gas and are appropriate for low-level health care providers.

Thermal ablation: Thermal ablation is a technology that uses a heated probe to destroy cells and tissue on the surface of the cervix, typically at temperatures 100-120 °C. This technique is relatively low cost and considered appropriate for low- to mid-level providers. Thermal ablation is increasingly being adopted as an alternative to cryotherapy. New thermal ablation devices can be used with portable battery packs for use at the point of care.

b For advanced lesions and suspicion of invasive cervical cancer, women should be referred to an appropriate facility for further management.

Large Loop Excision of the Transformation Zone (LLETZ): LLETZ uses a wire loop heated by electric current to remove cells and tissue on the surface of the cervix. LLETZ 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.

TABLE 4 Emerging and improved treatment devices

Name	Developer	Description	Treatment time	Development stage
CryoPen	CryoPen Inc.	POC – electricity-based, battery-based cryotherapy device	15 minutes	FDA
CryoPop	Momo Scientific / Jhpiego	low gas requirement cryotherapy device	15 minutes	In development
Thermocoagulator	Cure Medical Global (formerly Liger)	POC – battery-driven thermocoagulator	1 minute	FDA 510(k)
C3 Mobile Thermocoagulator	WiSAP	POC – electricity-based, battery-based thermocoagulator device	1 minute	CE

Source: communication from manufacturers and manufacturer websites

CryoPop (Momo Scientific, USA)

developed in collaboration with Jhpiego, a John's Hopkins University-affiliated NGO, aims to replace traditional cryotherapy devices to increase access and reduce the cost per treatment. This device uses about 1/10 of the amount of gas used in traditional cryotherapy. CryoPop is currently undergoing clinical evaluation.[32]

CryoPen (CryoPen Inc ,USA)

uses electricity to freeze a metal rod which is then applied to the cervix in the same way as a cryogun. It can also run on a car battery when electricity is not available thus representing the advantage that cryotherapy does not depend on gas supplies.[33] CryoPen has been FDA approved for treatment of CIN 1,2,3.[34]

Figure 12: Cryopen

© CryoPen Inc

Figure 13: C3 Mobile Thermocoagulator
© WiSAP

C3 Mobile Thermocoagulator (WiSAP, Germany)

uses heat to destroy tissue. The superficial epithelium blisters off after treatment and the underlying stroma and glandular crypts are destroyed by desiccation. The temperature for treatment of CIN is 100-120°C. The C3 Mobile Thermocoagulator is designed for LMICs and can run on electricity or battery pack.[35]

Figure 14: Thermocoagulator
© Cure Medical Global

Thermocoagulator (Cure Medical Global, formerly Liger Medical LLC, USA)

has been developed with support from PATH to overcome cryotherapy challenges with a small, portable device run on battery. It has received US FDA clearance and is commercially available. A study comparing efficacy of Liger Thermocoagulator with cryotherapy and LLETZ will be undertaken in Zambia. Primary outcome results are expected in August 2019.[36]

BARRIERS TO ACCESS

To reduce the barriers to screening and treatment, emerging tools must be accessible and appropriate for LMIC settings.[37,38,39] These settings typically require a more robust design and easy-to-use interface with less reliance on fixed infrastructure (electricity, gas, transport). New technologies must be clinically validated, preferably certified by a stringent international regulatory body. Where laboratory facilities are available, test and treatment costs must be affordable. For many women, access to screening can be improved through specimen self-collection. Furthermore, loss-to-follow-up can be reduced when validated POC technologies are made available. Finally, linkage to appropriate care and management must be ensured for women with more advanced lesions and cancer.

Improved technology is only part of the solution to reduce cervical cancer: high screening coverage and an organized screening programme are also necessary. Scale up of national population-based screen-and-treat programmes is needed globally, particularly in LMICs. Even where there is strong political support to scale-up cervical cancer services, awareness campaigns and demand creation can play a significant role for coverage. To achieve reduced mortality and to move more quickly toward the 2030 WHO elimination targets, strategies for secondary prevention of cervical cancer need to sit in complement to parallel primary and tertiary prevention efforts.

TABLE 5 Access barriers for Cervical Cancer

Market drivers	Access barriers
Innovation and Availability	• Investments needed for development and validation of new screening tests: HPV DNA and biomarker tests, digital cervicography tools • Investments needed for development and validation of new technologies for CIN treatment: cryotherapy and thermal ablation • Tests and devices need to be simple, automated, and safe for POC use in LMICs • Evidence needed for effective and appropriate clinical algorithms
Affordability	• POC HPV DNA tests are still too expensive for rollout in LMICs • Cost and cost-effectiveness is an issue also for new technologies and algorithms • Cost reductions or investment for new technology rollout when market is small

Market drivers	Access barriers
Quality	• Few tests have been submitted to the WHO prequalification programme • New tests and devices lack adequate validation in LMIC settings • Regulatory approval of self-collection devices
Demand and Adoption	• Operations research needed for impact and cost-effectiveness in LMICs • WHO recommendations and national policy for adoption of new technologies and uptake of new algorithms • Global forecasting required for tests and devices (particularly HPV DNA tests) • In-country awareness, clinician endorsement, and demand generation for high-quality tests
Supply and Delivery	• Expensive infrastructure and training required for existing technologies • Cryotherapy tools require high levels of infrastructure (gas, electricity, transport) • Lack of network coordination resulting in stock-outs, loss-to-follow-up

CONCLUSION

Cervical cancer is one of the most preventable and curable 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, treatments provide effective outpatient intervention, reducing unnecessary morbidity and mortality associated with more advanced stages of cancer.

For secondary prevention strategies to be effective, validated screening tests and treatment procedures must be widely available and implemented at the programmatic level. The large health disparities for cervical cancer prevention in LMICs reflect barriers of access to healthcare, lack of technologies appropriate for LMIC settings and disparities in the delivery of screening and other prevention services. These barriers must be addressed in order to meet the WHO 2030 cervical cancer elimination goals.

APPENDIX

A. HPV TESTING

Assay	*Real*Time High Risk (HR) HPV
Platform	m2000 sp/rt
Manufacturer/Developer	Abbott
Test target	HPV DNA (L1 gene) target amplification
Genotypes	HPV16, 18 (individual); 12 other HR: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
Sample type (approved)	Cervical specimens in: • PreservCyt • SurePath preservative fluid • Abbott Cervi-Collect specimen collection kit
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	FDA/CE/HC/TGA/PMDA
8 hour throughput	96

Assay	Alinity m High Risk (HR) HPV
Platform	Alinity m
Manufacturer/Developer	Abbott
Test target	HPV DNA (L1 gene) Target Amplification
Genotypes	HPV 16, 18, 45 (individual) 2 other HR groups: A) 31, 33, 52, 58, B) 35, 39, 51, 56, 59, 66, 68
Sample type (approved)	Cervical specimens in: • PreservCyt • SurePath Preservative Fluid • Abbott Cervi-Collect Specimen Collection Kit
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE
8 hour throughput	Alinity m High Risk (HR) HPV

Assay	cobas® 4800 HPV
Platform	4800
Manufacturer/Developer	Roche
Test target	HPV DNA (L1 gene) target amplification
Genotypes	HPV 16, 18 (individual) 12 other HR: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
Sample type (approved)	Cervical specimens in: • PreservCyt • SurePath Preservative Fluid • Roche Cell Collection Medium • cobas PCR Cell Collection Media
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	FDA / CE / HC / TGA (Note: only US-FDA approved test for primary screening)
8 hour throughput	192

Assay	cobas® HPV (6800/8800)
Platform	6800/8800
Manufacturer/Developer	Roche
Test target	HPV DNA (L1 gene) target amplification
Genotypes	HPV 16, 18 (individual) 12 other HR: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
Sample type (approved)	Cervical specimens in: • PreservCyt • SurePath Preservative Fluid • Roche Cell Collection Medium • cobas PCR Cell Collection Media
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE
8 hour throughput	384/960

Assay	*Aptima HPV*
Platform	Panther
Manufacturer/Developer	Hologic
Test target	E6, E7mRNA Target Amplification
Genotypes	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 (not individual)
Sample type (approved)	Cervical Specimen in PreservCyt
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	FDA / CE / HC / TGA / PMDA
8 hour throughput	275

Assay	Cervista HPV 16/18 assay
Platform	thermal cycler + plate reader
Manufacturer/Developer	Hologic
Test target	HPV DNA (L1, E6, E7) Signal Amplification
Genotypes	HPV 16, 18 (individual)
Sample type (approved)	Cervical Specimens in PreservCyt® Solution ThinPrep® Pap Test using Broom-type device (e.g. Rovers Cervex® Brush, Wallach Papette®), or Endocervical Brush/Spatula
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	FDA / TGA
8 hour throughput	TBC

Assay	Onclarity HPV Assay
Platform	Viper LT System
Manufacturer/Developer	Becton Dickinson and Company
Test target	HPV DNA (E6/E7) Target Amplification
Genotypes	HPV types 16, 18, 31, 45, 51, 52 (individual); 8 other genotypes in three groups (33/58, 56/59/66, 35/39/68)
Sample type (approved)	Cervical specimens in: • BD SurePath Preservative Fluid • iHologic PreservCyt® Preservative Fluid • BD HPV diluent co-collection media
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	FDA / CE / HC / TGA / PMDA
8 hour throughput	90

Assay	Digene Hybrid Capture 2 High-Risk HPV DNA test
Platform	Modular system (semi-automated) and Rapid Capture (automated high throughput)
Manufacturer/Developer	Qiagen
Test target	Whole Genome Probe HPV DNA Signal Amplification
Genotypes	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 (not individual)
Sample type (approved)	Cervical specimens in: • digene specimen transport media • PreservCyt Solution • SurePath Preservative Fluid
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	FDA / CE / HC / TGA / ?
8 hour throughput	Up to 352

Assay	*care*HPV
Platform	careHPV Test System
Manufacturer/Developer	Qiagen
Test target	HPV DNA Signal Amplification
Genotypes	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 (not individual)
Sample type (approved)	Cervical Specimen in careHPV Collection Media
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE / WHO PQ
8 hour throughput	Up to 270

Assay	Xpert® HPV
Platform	GeneXpert (IV, XVI, Infinity-48, Infinity-80)
Manufacturer/Developer	Cepheid
Test target	HPV DNA (L1 gene) Target Amplification
Genotypes	HPV 16, 18/45 (specific identification) 11 other HR: 31, 33, 35, 39, 51, 52, 56, 58, 59, 66, 68
Sample type (approved)	Cervical Specimen in PreservCyt ThinPrep liquid cytology specimens
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	/ CE / HC / TGA / ? WHO PQ
8 hour throughput	32, 128, 384, 640

Assay	Harmonia HPV
Platform	Aurtrax extractor + Life 96 PCR System
Manufacturer/Developer	LifeRiver Biotech
Test target	HPV DNA
Genotypes	HPV 16, 18 (individually) 12 other hr: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
Sample type (approved)	genital swabs
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE
8 hour throughput	384

Assay	Venus HPV
Platform	Aurtrax extractor + Life 96 PCR System
Manufacturer/Developer	LifeRiver Biotech
Test target	HPV DNA
Genotypes	15 hrHPV: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 59, 66, 68, 82 (collectively and individually)
Sample type (approved)	genital swabs
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE
8 hour throughput	384

Assay	GynTect methylation PCR assay
Platform	Abi7300 or Abi7500 thermalcycler Roche Cobas z480
Manufacturer/Developer	oncgnostics GmbH
Test target	6 Methylated Human DNA regions
Genotypes	NA
Sample type (approved)	Cervical Sample in STM, PreservCyt or SureThin
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE-IVD
8 hour throughput	

Assay	QIAsure Methylation Test PCR kit
Platform	Rotor-Gene Q MDx* *Note need to do DNA extraction, bisulfite conversion and measure DNA concentration before PCR
Manufacturer/Developer	Self-screen B.V. / QIAGEN
Test target	2 Methylated Human Genes
Genotypes	NA
Sample type (approved)	Cervical swabs in PreservCyt or STM Self-collected Vaginal Samples in PreservCyt
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE-IVD
8 hour throughput	70 samples per run

Assay	MeltPro® High Risk HPV Genotyping Assay
Platform	Thermal cycler
Manufacturer/Developer	QuanDx
Test target	PV DNA Target amplification
Genotypes	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 (individual)
Sample type (approved)	Cervical swab
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE
8 hour throughput	

Assay	HPV OncoTect® E6, E7 3Dx mRNA assay
Platform	Flow Cytometer
Manufacturer/Developer	InCellDX
Test target	HPV E6/E7 mRNA
Genotypes	High risk
Sample type (approved)	Cervical swab
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE
8 hour throughput	up to 100 samples in 5 hours

Assay	OncoE6™
Platform	NA
Manufacturer/Developer	Arbor Vita
Test target	E6 onco-protein Test
Genotypes	HPV 16,18
Sample type (approved)	Cervical swab
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE
8 hour throughput	

Assay	Prevo-Check
Platform	NA
Manufacturer/Developer	Abviris
Test target	anti-HPV 16 serology
Genotypes	HPV 16
Sample type (approved)	blood/serum
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE** approved only for detection of HPV16-induced head/neck and anogenital carcinomas currently
8 hour throughput	

Assay	NUCLISENS® EASYQ® HPV (discontinued)
Platform	EasyQ
Manufacturer/Developer	Biomerieux
Test target	HPV mRNA (E6/E7) Signal Amplification
Genotypes	HPV types 16, 18, 31, 33, and 45
Sample type (approved)	
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	CE
8 hour throughput	

Assay	Q-CAS HPV (in development)
Platform	Q-POC
Manufacturer/Developer	QuantuMDx/ Global Good
Test target	HPV DNA Target amplification
Genotypes	13 high risk
Sample type (approved)	Cervical swab
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	NA
8 hour throughput	TBD

Assay	Truenat HPV-HR (in development)
Platform	Truelab PCR analyzer
Manufacturer/Developer	Molbio
Test target	HPV DNA Target amplification
Genotypes	TBD
Sample type (approved)	TBD
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	NA
8 hour throughput	TBD

Assay	Ampfire HPV (in development)
Platform	
Manufacturer/Developer	Atila Biosystems
Test target	HPV DNA isothermal amplification
Genotypes	15 hrHPV (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 59, 66, 68, 82); HPV16/18 individually
Sample type (approved)	genital swabs
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	NA
8 hour throughput	TBD

Assay	NEDxA (in development)
Platform	
Manufacturer/Developer	Genomica
Test target	HPV DNA
Genotypes	
Sample type (approved)	
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	NA
8 hour throughput	TBD

Assay	CerMarkTM Cervical Cancer Screen (in development)
Platform	
Manufacturer/Developer	OncoGenesis
Test target	Onco-protein Test
Genotypes	
Sample type (approved)	
Regulatory Approval (US, EU, Canada, Australia, Japan, WHO PQ)	NA
8 hour throughput	CerMarkTM Cervical Cancer Screen

B. SELF-SAMPLING PRODUCTS

Product name	**careBrush®**
Manufacturer	**Qiagen**
Sample collection type	Brush
Transport media	*care*HPV collection Medium
Pack size	50
Kit	Pre-scored brushes (1ml *care*HPV media provided separately)
Regulatory approval	CE-IVD
Stability (storage and transport)	15-30°C for 14 days; 2-8°C for 30 days

Product name	**Qvintip™**
Manufacturer	**Aprovix AB**
Sample collection type	Swab
Transport media	Dry or PreservCyt or Sample Transport Media Solution
Pack size	
Kit	Sample collection device of complete kit: single use, blue and white self-sampling swab stick, sample storing tube with bar code and cap, instructions for use and request form, blank self-adhesive label, response envelope
Regulatory approval	CE-mark
Stability (storage and transport)	As soon as possible (wihtin 24 to 48 hours)

Product name	**SelfCerv**
Manufacturer	**Hologic/Ilex**
Sample collection type	Tampon
Transport media	PreservCyt
Pack size	
Kit	individually packed tampon and collection vial
Regulatory approval	In development
Stability (storage and transport)	TBC

Product name	**HerSwab™**
Manufacturer	**Eve Medical Inc.**
Sample collection type	Brush
Transport media	Dry or liquid media
Pack size	
Kit	single use, tampon-like brush applicator device plus separate tube
Regulatory approval	Class II MDL (Health Canada)
Stability (storage and transport)	24 to 48 hrs

Product name	**Viba Brush®**
Manufacturer	**Rover Medical Devices**
Sample collection type	Brush
Transport media	Dry
Pack size	
Kit	Single use Sample Collection device with transport vial
Regulatory approval	CE-mark
Stability (storage and transport)	within 24 to 48 hours

Product name	**Evalyn Brush®**
Manufacturer	**Rover Medical Devices**
Sample collection type	Brush
Transport media	Liquid media
Pack size	
Kit	Single use all-in-one - brush/applicator transport medium
Regulatory approval	CE- mark
Stability (storage and transport)	4-30°C up to 32 weeks

Product name	**Delphi Screener**
Manufacturer	**Rover Medical Devices**
Sample collection type	Lavage
Transport media	Liquid media
Pack size	
Kit	single use sterile lavage applicator device plus separate tube
Regulatory approval	CE-mark
Stability (storage and transport)	within 24 hours

Product name	**FLOQSwabs™**
Manufacturer	**Copan Flock Technologies SRL, part of Copan Diagnostics Inc.**
Sample collection type	Swab
Transport media	Dry media or Universal Transport Medim (UTM™)
Pack size	50 (6 x 50 packs per box)
Kit	single use kit, comprises the cotton tipped swab enclosed in a plastic tube within a ziplock bag packaged with or without UTM™
Regulatory approval	CE mark for professional use
Stability (storage and transport)	Room Temperature or refrigerated (2-8°C), within 48 hours; longer if frozen at (-20° C)

Product name	**Cobas Uni Swab**
Manufacturer	**Roche**
Sample collection type	Swab
Transport media	Can use either SurePath Collection Media or Hologic ThinPrep PreservCyt Solution
Pack size	
Kit	Individually packaged
Regulatory approval	CE -marked (Hologic PreservCyt); FDA approved (SurePath)
Stability (storage and transport)	Transport at 2-30° C and stable within 90 days

Product name	**Plain Sterile Swab**
Manufacturer	**NA - Generic (e.g. Dacron cotton Swab)**
Sample collection type	Swab
Transport media	Liquid Media
Pack size	
Kit	Separate or complete kit: sterile Dacron cotton swab, and sterile tube containing STM
Regulatory approval	
Stability (storage and transport)	within 3 weeks from sample collection

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