Risk Management and Healthcare Policy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

An Overview of HPV Screening Tests to Improve Access to Cervical Cancer Screening Amongst Underserved Populations: From Development to Implementation

Kehinde S Okunade[1], Adebola A Adejimi[2], Sarah O John-Olabode[3], Yusuf A Oshodi[4], Ayodeji A Oluwole[1]

[1]Department of Obstetrics & Gynaecology, College of Medicine, University of Lagos, Lagos, Nigeria; [2]Department of Community Health and Primary Care, College of Medicine, University of Lagos, Lagos, Nigeria; [3]Department of Haematology and Blood Transfusion, College of Medicine, University of Lagos, Lagos, Nigeria; [4]Department of Obstetrics & Gynaecology, Lagos State University College of Medicine, Lagos, Nigeria

Correspondence: Kehinde S Okunade, Department of Obstetrics and Gynaecology, College of Medicine, University of Lagos, Lagos, Nigeria, Email sokunade@unilag.edu.ng

Abstract: Cervical cancer is the most common human papillomavirus (HPV)-related disease. Knowledge of the natural history and aetiology of cervical cancer offers unique opportunities for its prevention, and the development of HPV screening tests is one of the most effective strategies. The current HPV diagnostics detect HPV DNA or E6/E7 mRNA in cervical/vaginal samples using molecular-based technologies. HPV screening tests are more sensitive than cytology or visual inspection with acetic acid (VIA) as a primary screening method and are even more clinically valuable in triaging mild cytological abnormalities as a hybrid test. As technical and laboratory resources are grossly limited in marginalized or underserved settings which thus require that women travel long distances for screening and treatment. The practical implementation of an HPV-based screening programme may face many challenges and measures should be instituted to overcome these challenges without compromising disease detection. These measures may include a reduction in screening frequency using the WHO global strategy of offering HPV screening tests at 35 and 45 years of age, adoption of a high throughput testing technology, and improved access to vaginal HPV self-sampling screening tests to women in remote settings or those who are reluctant to undergo gynecologic examination. Another important strategy is the implementation of a "see-and-treat" approach using a point-of-care platform that requires limited skills of laboratory technicians. In addition, the development and large-scale incorporation of more specific HPV testing technologies that are much cheaper and easier to use in non-laboratory settings than the currently available options should be prioritized for underserved settings. At the same time, there is a need to develop and commence the implementation of an affordable and readily available intermediate or secondary test with optimal specificity for triaging or segregating clinically unimportant HPV infections that do not require colposcopy.

Keywords: cervical cancer, cytology, E6/E7 mRNA, HPV self-sampling, VIA

Introduction

Cervical cancer is a major public health problem and is the fourth most common cancer in women worldwide accounting for an estimated 604,000 new cases each year.[1] More than 80% of the global burden of cervical cancer occurs in the low- and middle-income countries (LMIC) of sub-Saharan Africa and Asia, where it accounts for about 12% of all female cancers.[2] In 2020, an estimated 342,000 deaths were due to cervical cancer thus accounting for 7.5% of cancer-related deaths in females.[1] Nearly nine in ten of these deaths occur in the LMICs.[1,3] Knowledge of the natural history and aetiology of cervical cancer has now offered a unique opportunity to prevent the disease.[4] To eliminate the substantial global burden and the increasing inequity associated with cervical cancer, the World Health Organization (WHO) Director-General made a call in May 2018 for global action for the introduction of a triple-

Received: 26 March 2022
Accepted: 14 September 2022
Published: 23 September 2022

intervention strategy called 90–70–90 targets: (1.) to vaccinate 90% of all girls by age 15 years, (2.) to screen 70% of women twice by age 35 and 45 years, and (3.) to treat at least 90% of all precancerous and cancerous lesions detected during screening.[5] This is projected to result in a worldwide threshold of 4 new cases per 100,000 women-year corresponding to more than 74 million cases and more than 62 million deaths averted over the next century.[6] This suggests that cervical cancer is nearly completely preventable through highly effective primary (HPV vaccination) and secondary (screening) prevention measures.[1] In 2019, WHO recommends high-quality screening programs targeting women aged 30 to 49 years, such as visual inspection with acetic acid in resource-constrained settings, a Papanicolaou (Pap) smear test every 3 to 5 years, or HPV testing every 5 years, coupled with timely and effective treatment of precancerous lesions.[7] As emerging evidence currently supports the use of HPV-based tests as the preferred primary screening test for the detection of precancerous lesions,[5,8] there is an urgent need to build a more equitable future and eradicate the health-care disparities that may affect the effective introduction of this high-performance screening test[5] in underserved populations. Therefore, this review will focus on identifying these important challenges to testing and then propose effective strategies for its successful implementation.

The Link Between Human Papillomavirus and Cervical Cancer

Persistent genital infection with certain types of HPV has been reported as a necessary cause of cervical cancer.[9] The strength of the association between HPV infection and cervical squamous cell carcinoma is higher than that of the association reported between smoking and lung cancer.[10] HPV infections are, however, less commonly related to adenocarcinomas of the cervix as only about 43% of cases seen in women aged 60 years and older are associated with the infection.[10] HPV are closely related viruses that are classified and numbered based on their nucleic acid sequencing and order of discovery, respectively.[10] More than 200 HPV types are known to exist in humans[11,12] with about 30 of these transmitted during sexual contact to the genital areas where 14 types (classified as group 1 carcinogens) are associated with cervical cancer.[9] At least one of these HPV types is implicated in almost all cases of cervical squamous cell carcinoma.[9] As a result of its causal relationship with cervical cancer and its precursor lesions, genital HPV infection can be grouped as non-oncogenic and oncogenic HPV types.[9,10] Non-oncogenic HPV include types 6, 11, 42, 43, and 44 while the oncogenic types are 16, 18, 31, 33, 34, 39, 45, 51, 52, 56, 58, 59, 66, and 68.[9] The virus usually infects matured mucocutaneous epithelial cells of the cervix to produce viral particles that disrupt the normal cell-cycle control causing the promotion of uncontrolled cell division that leads to genetic damage.[11] In general, the development of a productive HPV-related lesion requires that the virus access the epithelial basal layer once the epithelial barrier has been breached.[13] The detection of oncogenic HPV infection in the cervix is necessary but may not be enough for the development of cervical cancer.[9] This is because most HPV-induced cervical changes are transient with about 90% clearing spontaneously within 2 years.[14] Therefore, the presence of factors that alter a woman's ability to clear the virus[10] such as an individual's genetic predisposition and immune status,[15] genetic variations in HPV types, infection with more than one oncogenic HPV type, and frequency of HPV reinfection[10] will determine whether or not the woman develops cervical cancer.

Basic Virology of HPV

HPV is a relatively small, non-enveloped virus of about 55 nm in diameter.[10] Each virus has an icosahedral capsid containing 72 capsomers with at least two capsid proteins, L1 and L2. Each of these capsomers is a pentamer of the major capsid protein, L1.[16] Each of the major virion capsids contains about 12 copies of the minor capsid protein, L2.[17] HPV consists of a single-molecule of circular, double-stranded DNA[18] with a genome containing all Open Reading Frame (ORF) protein-coding sequences confined to one of the strands.[19] The HPV genome consists of three functional regions:[19] (1.) The long control region (LCR) referred to as the "non-coding upstream regulatory region (URR)" contains the highest degree of variation in the HPV genome. It contains the p97 core promoter along with enhancer and silencer sequences that control ORFs transcription for the regulation of DNA replication;[20] (2.) The "early region (E)" consists of ORFs E1, E2, E4, E5, E6, and E7, which control viral replication and tumorigenesis; and (3.) The "late region (L)" encodes the L1 and L2 structural proteins for the viral capsid (Figure 1).[19] A new HPV type should have nucleotide

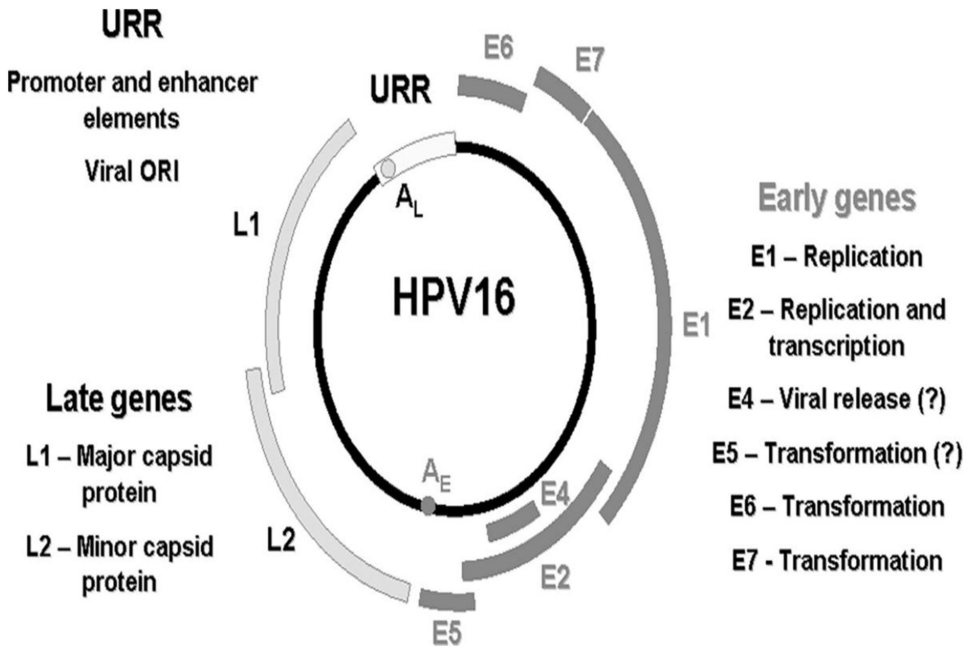

Figure 1 Basic virology of HPV. Used with permission of Portland Press, Ltd. from Stanley MA, Pett MR, Coleman N. HPV: from infection to cancer. *Biochem Soc Trans*. 2007;35(Pt 6):1456–1460; permission converyed through Copyright Clearance Center, Inc.[19]

sequences of the E6, E7, and L1 ORFs that are no more than 90% homologous to the corresponding sequences of any of the existing HPV type.[10]

Development of HPV Screening Tests

Cervical cancer screening involves testing for HPV infection and precursor cervical cancer lesions among women with no symptoms, and when screening detects cervical pre-cancerous lesions, treatment can easily be instituted, and cancer avoided.[10] The development of HPV screening tests is one of the most effective strategies for cervical cancer control.[10] The laboratory culture of HPV is not reliable; however, through the use of molecular-based technologies, HPV DNA or HPV E6/E7 mRNA can be detected in cervical/vaginal samples.[21] The molecular techniques for HPV DNA detection can be classified broadly into those technologies that are not amplified, such as direct genome detection tests or nucleic acid probe tests, and those that utilize amplification, both conventionally and in real-time, to obtain DNA copies. Amplification methods can also be divided into three different groups: (1.) *target amplification* – which involves amplification of the target nucleic acids (for example, polymerase chain reaction – PCR); (2.) *signal amplification* – which involves amplification of the signal generated from each probe by a compound-probe or branched-probe technology; and (3.) *probe amplification* – which involves the probe molecule amplification (for example, ligase chain reaction – LCR). Conversely to the DNA detection method, the mRNA tests identify the expression of HPV E6 and E7 oncoproteins that regulate the oncogenic process of cervical cancer. The detection of E6/E7 oncogene expression could be a more specific and better cancer risk predictor than the HPV-DNA tests.[22]

Many previous studies of HPV generally use nucleic acid amplification methods that generate genotype-specific results.[23] The PCR assays specifically target genetically conserved regions in the L1 gene to detect the HPV DNA of any of the 14 HPV types that are known to cause cervical cancer in cervical epithelial cells.[9] The detection of one or any combination of these HPV types will result in a positive test result. The assays for detecting HPV infection differ in their sensitivity and type-specificity,[22] depending on the anatomic region sampled, as well as the method of specimen collection.[24] Without the knowledge of specific HPV types in a screening sample, many women will undergo unnecessary follow-up and treatment as different HPV types carry a different risk of cervical cancer.[25] Virus-like-particle-(VLP)-based enzyme immunoassays are the most frequently used HPV serologic assays; however, there are no standardized

reagents for these assays in the laboratory and there are also no standards for setting a threshold for a positive result. Therefore, serology-based HPV tests are not used in clinical practice.[24] In addition, none of the commercially available molecular-based HPV tests is clinically indicated nor approved for use in men.[22]

Implementation of HPV Screening Tests

The most appropriate HPV test should be selected for use in a cervical cancer screening programme, especially in underserved settings based on consideration for performance accuracy, clinical validation, costs, and other operational and logistical requirements such as supply chain management and storage.[22] The direct detection of HPV DNA in cervical or vaginal samples should be used as an alternative or to complement a population-based cytological screening programme.[10] This is because HPV-based screening tests are more sensitive than cytology or VIA as a primary screening method and are even more clinically valuable for triaging mild cytological abnormalities as a hybrid test.[10] These screening strategies minimize the need for unnecessary follow-up evaluation, especially in settings with limited or no access to colposcopy.

(a) Hybrid HPV screening: Cervical cancer screening programmes in both developed and developing countries have relied mostly on cytological-based testing such as Pap smear tests. However, because of the lower specificity of Pap smear,[8,26,27] women with mild cytological abnormalities[10] such as atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesions (LSIL)[28,29] are required to undergo triaging using the more specific molecular-based HPV screening tests in a hybrid approach before referral for colposcopy if positive for any of the oncogenic HPV types. However, based on the timing of the triage screening test, hybrid HPV tests are classified as (1.) *Pap Smear/HPV co-test* involves the simultaneous performance of cervical cytology and HPV DNA testing using the sample of cells removed during a Liquid Based Cytology (LBC), and (2.) *HPV reflex testing* involves the performance of an HPV test using cells from the sample removed during an LBC. Women with mild cytological abnormalities who test negative for HPV infection will undergo repeat cytology testing after 12 months while those who test positive for any type-specific oncogenic HPV type(s) will be referred for immediate colposcopy evaluation.[30]

(b) Primary HPV test: This is using the HPV test as a first-line screening method. HPV tests have a higher sensitivity than cytology (96.1% vs 53.0%) but lower specificity (90.7% versus 96.3%).[8] Although it is highly sensitive, HPV testing cannot discriminate between transient and persistent infections,[31] and thus it is only better suited as a screening test.[32] The International Agency for Research on Cancer (IARC)[33] and the WHO[5] have now recommended HPV tests as the primary method for the detection of precancerous lesions of the cervix.[8] Therefore, the primary HPV screening test has now replaced other screening modalities in almost all developed countries and many developing countries.[8,31,34,35] Although, it has a higher cost than other screening tests, it is more cost-effective in detecting precancerous lesions of the cervix when implemented in an organised setting[8] that is accompanied by a strong health-infrastructure framework. A negative HPV test result provides better reassurance against the development of high-grade precancerous lesions with safe prolongation of screening intervals.[31] A negative test result indicates a low probability of developing high-grade precancerous and cancerous lesions in the next 5–10 years with high accuracy.[36] A secondary or intermediate test, therefore, needs to be developed and implemented to avoid the unnecessary, invasive, uncomfortable, and costly procedures that may accompany an HPV-based screening programme. This affordable and readily available test is essential to segregate or triage clinically unimportant HPV infections that do not require colposcopy[37] by optimizing specificity, without sacrificing sensitivity.[38,39] The search for the most appropriate test continues, however, in most parts of the world, the Pap smear test is currently used to triage oncogenic HPV-positive women who are negative for HPV16 or 18. Women who test positive for HPV infection are either referred directly for colposcopy (if positive for HPV types 16/18) or cervical cytology before colposcopy (if positive for one or any combination of the remaining 12 oncogenic HPV types) when necessary.[35] This is not yet a scalable solution; however, it is an important area that requires further investigation to identify the most suitable

intermediate or secondary test that would prevent low-risk patients from undergoing unnecessary invasive procedures or additional follow-up visits.

Overcoming Challenges of Implementation of HPV-Based Cervical Cancer Screening Programme in Underserved Populations

(a) Programmatic considerations: Cervical cancer is now primarily a disease of marginalized and underserved women, particularly those in the LMICs of Africa and Southeast Asia.[40] Currently, only 44% of women in resource-limited countries have ever been screened for cervical cancer, with the lowest prevalence (0.9–50.8%) among women in sub-Saharan Africa,[41] compared with over 60% in high-income countries (HIC).[6] The underserved women in these resource-limited countries often lack access to the resources necessary to implement successful cervical cancer prevention programmes.[4] In addition, these countries often have limited funds and cancer screening programs usually compete with other pressing health needs.[42] Furthermore, women who are at the highest risk of cervical cancer in most LMIC settings often lack access to relevant information and services necessary to protect them from developing the disease.[33]

(b) Challenges of HPV-based screening implementation: There has been a gradual shift from HPV reflex testing for mild cytological abnormalities to Pap smear/HPV co-test paradigm, and now to primary HPV testing.[31] All these screening approaches face common challenges to successful implementation such as logistic and infrastructure inadequacies, cost concerns, poor follow-up, and sociocultural constraints.[43] A broad array of social, cultural, and clinical factors may influence where, how, or if cervical cancer screening services can be successfully provided. Even though HPV-based screening programmes have various advantages, the practical implementation is fraught with substantial challenges, especially in resource-limited settings.[43] HPV-based screening programmes face multiple choices regarding the programme design such as the choice of HPV test, triage method, follow-up and referral recommendation, target age range, screening interval, communication strategy, and training strategy for health-care providers.[44] The optimal choices in underserved settings will, therefore, depend on the national and local context, including the availability of financial resources, technical capacity and laboratory infrastructure.[44,45] Regardless of the chosen testing method, it is important to ensure that women with screen-positive precancerous and cancerous lesions be adequately treated as it is unethical to offer screening without access to treatment.[5]

(c) Overcoming implementation challenges of HPV-based screening tests: Despite its cost-effectiveness, an HPV-based screening test per see is not enough to overcome the challenges of a fragile health-care structure. Before incorporating HPV tests into a screening programme, a thorough understanding of the complexities of the test must be carefully considered. In addition to its higher sensitivity than other available screening tests, the major advantage of HPV testing is its high and long-lasting negative predictive value and its extended screening intervals of at least 5 years.[8] The American Cancer Society, therefore, recommends that women initiate cervical cancer screening at age 30 years (or 25 years for average-risk persons) and undergo primary HPV testing every 5 years through age 65 years as a preferred option.[46] To further minimize the cost and frequency of testing without compromising disease detection, especially in settings with limited screening capacity, WHO has recommended, as part of its global strategies to eliminate cervical cancer, that a woman undergoes two HPV screening tests at 35 and 45 years of age to confer substantial lifetime preventive benefit.[5,47] Until recently, the major obstacles to the use of HPV-based molecular testing in most resource-constrained settings are the need for expensive laboratory infrastructure and the prolonged time required to process test results.[10] The development of the rapid molecular-based testing methods screening for cervical cancer screening is a milestone for the low-resource settings due to the high laboratory throughput and unnecessary requirements for huge infrastructure.[36] Furthermore, HPV screening tests now offer a unique opportunity for self-sampling to women who live in remote areas or who are reluctant to undergo gynaecological examination for sample collection by physicians.[48] Self-sampled HPV testing offers a cost-effective screening strategy by increasing the level of screening attendance, lowering the cost of testing, and attracting more unscreened or under-screened women.[49,50] Finally, to overcome the substantial loss to follow-up in women undergoing repeat cervical cancer screenings for monitoring, HPV-based tests can now be

safely implemented using a "see-and-treat" approach in a point-of-care platform that requires limited skills of laboratory technicians.[51] In this instance, HPV screening, triage, and treatment can be provided together in one visit.[5,47]

Conclusion

In recent years, the incidence and deaths from cervical cancer have decreased significantly in high-income countries (HICs) mostly due to the widespread implementation of screening programmes.[9] However, only 44% of women in LMICs have ever been screened[41] compared with over 60% in HICs.[6] WHO now recommends that women be screened regularly for cervical disease with a high-performance test such as an HPV-based molecular test and this is to replace the widely used Pap smear and visual inspection with acetic acid (VIA).[5] However, there are several challenges facing the practical implementation of an HPV-based screening programme in underserved settings such as the choice of HPV test, triage method, target age range, screening interval, follow-up and referral recommendation, communication strategies, non-availability of financial resources, technical capacity, and laboratory infrastructure.[44,45] Proposed measures to overcome these challenges without compromising disease detection in women in underserved settings include a reduction in screening frequency using the WHO global strategy by offering screening only twice to women at 35 and 45 years of age,[5,47] rapid turnover time of test results,[10] improved access to vaginal self-sampling HPV testing for women in remote settings or those who are reluctant to undergo gynaecological examination,[48] and implementation of a "see-and-treat" approach using a point-of-care platform that required limited skills of laboratory technicians.[51] All these strategies will be of substantial benefit to underserved populations, especially among women living in remote areas of Africa and Southeast Asia, where women may need to travel long distances for screening and treatment, and where there are limited or no access to technical and laboratory resources. In addition, the development and large-scale incorporation of more specific HPV testing technologies that are much cheaper and easier to use in non-laboratory settings than the currently available options should be prioritized for underserved settings. At the same time, there is a need to develop and commence the implementation of an affordable and readily available intermediate or secondary test with optimal specificity for triaging or segregating clinically unimportant HPV infections that do not require colposcopy.[37]

Acknowledgments

This work was supported in part through the protected time offered by the Fogarty International Center of the National Institutes of Health (under Award Numbers K43TW011930, D43TW010934, D43TW010134, and D43TW010543). The views expressed in this publication are those of the authors and do not necessarily reflect the official views of the National Institutes of Health.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Mohammed SI, Ren W, Flowers L, et al. Point-of-care test for cervical cancer in LMICs. *Oncotarget*. 2016;7(14):18787–18797. doi:10.18632/oncotarget.7709
3. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health*. 2020;8(2):e191–e203. doi:10.1016/S2214-109X(19)30482-6
4. Denny L. Cervical cancer: prevention and treatment. *Discov Med*. 2012;14(75):125–131.
5. World Health Organization. global strategy to accelerate the elimination of cervical cancer as a public health problem; 2020. Available from: http://apps.who.int/bookorders. Accessed September 14, 2022.
6. Canfell K, Kim JJ, Brisson M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet*. 2020;395(10224):591–603. doi:10.1016/S0140-6736(20)30157-4
7. World Health Organization. WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions; 2019.
8. Ronco G, Dillner J, Elfström KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet*. 2014;383(9916):524–532. doi:10.1016/S0140-6736(13)62218-7
9. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189(1):12–19. doi:10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F

10. Okunade KS. Human papillomavirus and cervical cancer. *J Obstet Gynaecol*. 2020;40(5):602–608. doi:10.1080/01443615.2019.1634030
11. Unger ER, Barr E. Human papillomavirus and cervical cancer. *Emerg Infect Dis*. 2004;10(11):2031–2032. doi:10.3201/eid1011.040623_09
12. Burd EM. Human papillomavirus and cervical cancer. *Clin Microbiol Rev*. 2003;16(1):1–17. doi:10.1128/CMR.16.1.1-17.2003
13. Schiffman M, Doorbar J, Wentzensen N, et al. Carcinogenic human papillomavirus infection. *Nat Rev Dis Primers*. 2016;2(1):16086. doi:10.1038/nrdp.2016.86
14. Quinlan JD. Human papillomavirus: screening, testing, and prevention. *Am Fam Physician*. 2021;104(2):152–159.
15. de Araujo Souza PS, Villa LL. Genetic susceptibility to infection with human papillomavirus and development of cervical cancer in women in Brazil. *Mutat Res*. 2003;544(2–3):375–383. doi:10.1016/j.mrrev.2003.06.013
16. Baker TS, Newcomb WW, Olson NH, Cowsert LM, Olson C, Brown JC. Structures of bovine and human papillomaviruses. Analysis by cryoelectron microscopy and three-dimensional image reconstruction. *Biophys J*. 1991;60(6):1445–1456. doi:10.1016/S0006-3495(91)82181-6
17. Sapp M, Volpers C, Müller M, Streeck RE. Organization of the major and minor capsid proteins in human papillomavirus type 33 virus-like particles. *J Gen Virol*. 1995;76(Pt 9):2407–2412. doi:10.1099/0022-1317-76-9-2407
18. Favre M. Structural polypeptides of rabbit, bovine, and human papillomaviruses. *J Virol*. 1975;15(5):1239–1247. doi:10.1128/JVI.15.5.1239-1247.1975
19. Stanley MA, Pett MR, Coleman N. HPV: from infection to cancer. *Biochem Soc Trans*. 2007;35(Pt 6):1456–1460. doi:10.1042/BST0351456
20. Apt D, Watts RM, Suske G, Bernard HU. High Sp1/Sp3 ratios in epithelial cells during epithelial differentiation and cellular transformation correlate with the activation of the HPV-16 promoter. *Virology*. 1996;224(1):281–291. doi:10.1006/viro.1996.0530
21. Dabeski D, Duvlis S, Basheska N, et al. Comparison between HPV DNA testing and HPV E6/E7 MRNA testing in women with squamous cell abnormalities of the uterine cervix. *Pril*. 2019;40(1):51–58. doi:10.2478/prilozi-2019-0003
22. Cuzick J, Cadman L, Mesher D, et al. Comparing the performance of six human papillomavirus tests in a screening population. *Br J Cancer*. 2013;108(4):908–913. doi:10.1038/bjc.2013.22
23. Okunade KS, Nwogu CM, Oluwole AA, Anorlu RI. Prevalence and risk factors for genital high-risk human papillomavirus infection among women attending the outpatient clinics of a university teaching hospital in Lagos, Nigeria. *Pan Afr Med J*. 2017;28. doi:10.11604/pamj.2017.28.227.13979.
24. Meites E, Gee J, Unger E, Markowitz L. Human Papillomavirus: chapter 11. In: *Epidemiology and Prevention of Vaccine-Preventable Disease*. 14th ed.; 2021. Available from: https://www.cdc.gov/vaccines/pubs/pinkbook/hpv.html.
25. Bonde JH, Sandri MT, Gary DS, Andrews JC. Clinical utility of human papillomavirus genotyping in cervical cancer screening: a systematic review. *J Low Genit Tract Dis*. 2020;24(1):1–13. doi:10.1097/LGT.0000000000000494
26. Wright TC. HPV DNA testing for cervical cancer screening. *Int J Gynaecol Obstet*. 2006;95(Suppl 1):S239–S246. doi:10.1016/S0020-7292(06)60039-8
27. Cuzick J, Clavel C, Petry KU, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer*. 2006;119(5):1095–1101. doi:10.1002/ijc.21955
28. Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol*. 2013;121(4):829–846. doi:10.1097/AOG.0b013e3182883a34
29. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol*. 2012;137(4):516–542. doi:10.1309/AJCPTGD94EVRSJCG
30. Massad LS, Xie X, D'Souza G, et al. Incidence of cervical precancers among HIV-seropositive women. *Am J Obstet Gynecol*. 2015;212(5):606.e1–8. doi:10.1016/j.ajog.2014.12.003
31. Bhatla N, Singhal S. Primary HPV screening for cervical cancer. *Best Pract Res Clin Obstet Gynaecol*. 2020;65:98–108. doi:10.1016/j.bpobgyn.2020.02.008
32. Wright TC, Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol*. 2007;197(4):346–355. doi:10.1016/j.ajog.2007.07.047
33. Bouvard V, Wentzensen N, Mackie A, et al. The IARC perspective on cervical cancer screening. *N Engl J Med*. 2021;385(20):1908–1918. doi:10.1056/NEJMsr2030640
34. Leinonen MK, Nieminen P, Lönnberg S, et al. Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland. *BMJ*. 2012;345:e7789. doi:10.1136/bmj.e7789
35. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. *Gynecol Oncol*. 2015;136(2):178–182. doi:10.1016/j.ygyno.2014.12.022
36. Catarino R, Petignat P, Dongui G, Vassilakos P. Cervical cancer screening in developing countries at a crossroad: emerging technologies and policy choices. *World J Clin Oncol*. 2015;6(6):281–290. doi:10.5306/wjco.v6.i6.281
37. Tota JE, Bentley J, Blake J, et al. Approaches for triaging women who test positive for human papillomavirus in cervical cancer screening. *Prev Med*. 2017;98:15–20. doi:10.1016/j.ypmed.2016.11.030
38. Rijkaart DC, Berkhof J, van Kemenade FJ, et al. HPV DNA testing in population-based cervical screening (VUSA-Screen study): results and implications. *Br J Cancer*. 2012;106(5):975–981. doi:10.1038/bjc.2011.581
39. Castle PE, Gage JC, Wheeler CM, Schiffman M. The clinical meaning of a cervical intraepithelial neoplasia grade 1 biopsy. *Obstet Gynecol*. 2011;118(6):1222–1229. doi:10.1097/AOG.0b013e318237caf4
40. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. *Lancet*. 2019;393(10167):169–182. doi:10.1016/S0140-6736(18)32470-X
41. Lemp JM, de Neve JW, Bussmann H, et al. Lifetime prevalence of cervical cancer screening in 55 low- and middle-income countries. *JAMA*. 2020;324(15):1532–1542. doi:10.1001/jama.2020.16244
42. World Health Organiation. Cervical cancer control in developing countries: memorandum from a WHO meeting. *Bull World Health Organ*. 1996;74(4):345–351.
43. Pimple SA, Mishra GA. Global strategies for cervical cancer prevention and screening. *Minerva Ginecol*. 2019;71(4):313–320. doi:10.23736/S0026-4784.19.04397-1
44. Arrossi S, Thouyaret L, Laudi R, et al. Implementation of HPV-testing for cervical cancer screening in programmatic contexts: the Jujuy demonstration project in Argentina. *Int J Cancer*. 2015;137(7):1709–1718. doi:10.1002/ijc.29530

45. Zhao Y, Bao H, Ma L, et al. Real-world effectiveness of primary screening with high-risk human papillomavirus testing in the cervical cancer screening programme in China: a nationwide, population-based study. *BMC Med*. 2021;19(1):164. doi:10.1186/s12916-021-02026-0
46. Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020;70(5):321–346. doi:10.3322/caac.21628
47. Bosch FX, Robles C, Díaz M, et al. HPV-FASTER: broadening the scope for prevention of HPV-related cancer. *Nat Rev Clin Oncol*. 2016;13 (2):119–132. doi:10.1038/nrclinonc.2015.146
48. Arbyn M, Smith SB, Temin S, Sultana F, Castle P; Collaboration on Self-Sampling and HPV Testing. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. *BMJ*. 2018;363:k4823. doi:10.1136/bmj.k4823.
49. Malone C, Barnabas RV, Buist DSM, Tiro JA, Winer RL. Cost-effectiveness studies of HPV self-sampling: a systematic review. *Prev Med*. 2020;132:105953. doi:10.1016/j.ypmed.2019.105953
50. Mezei AK, Armstrong HL, Pedersen HN, et al. Cost-effectiveness of cervical cancer screening methods in low- and middle-income countries: a systematic review. *Int J Cancer*. 2017;141(3):437–446. doi:10.1002/ijc.30695
51. Thomsen LT, Kjær SK. Human papillomavirus (HPV) testing for cervical cancer screening in a middle-income country: comment on a large real-world implementation study in China. *BMC Med*. 2021;19(1):165. doi:10.1186/s12916-021-02051-z