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IPVS policy statement on HPV nucleic acid testing guidance for those utilising/considering HPV as primary precancer screening: Quality assurance and quality control issues

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ABSTRACT

We advise that only clinically validated HPV assays which have fulfilled internationally accepted performance criteria be used for primary cervical screening. Further, assays should be demonstrated to be fit for purpose in the laboratory in which they will ultimately be performed, and quality materials manuals and frameworks will be helpful in this endeavor. Importantly, there is a fundamental shortage of well validated, low-cost, low complexity HPV tests that have demonstrated utility in a near-patient setting; representing a significant challenge and focus for future development in order to reach the WHO's goal of eliminating cervical cancer.

1. Call to action for global cervical cancer elimination strategy endorsed at 73rd World Health Assembly of the WHO

On May 18th, 2018, the WHO Director General Dr Tedros Adhanom Ghebreyesus made a call to action for cervical cancer elimination as a public health problem [1]. At the closure of the 73rd World Health Assembly of the WHO, a virtual meeting was held on November 17th, 2020, at which the official announcement of the global elimination strategy to accomplish this objective was launched. Three pillars of action as a strategy to achieve this were described, including, utilising a high precision assay for cervical screening in at least 70% of women worldwide with at least two lifetime screenings at 35 and 45 years of age, 90% of young girls completing an HPV vaccinate series by 15 years of age and 90% of women recognised with cervical disease receiving adequate care and treatment, including palliative care. Together these comprise the 2030 targets aimed at cervical cancer becoming a rare disease affecting <4/100,000 women per annum. Although we do have the tools to achieve this goal, the COVID-19 pandemic that began March 2020, has raised additional challenges.

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2. One pillar of action: increased coverage of cervical screening with high precision assays

Cervical cytology, as first described by George Papanicolaou in 1928 [2], performs well when adopted repeatedly (but has a poor negative predictive value when the frequency is greater than three yearly) for the target population and is implemented in a setting with high quality assurance (QA) and control (QC) and appropriate and timely follow up of cervical abnormalities. However, one-time cervical cytology has relatively low sensitivity and greatest effectiveness occurs due to the cumulative sensitivity associated with recurrent screening. The reality for those (few) women in Low and Middle Income Countries [LMICs] able to access cytology services is one to two cytology tests per lifetime. Often when LMICs have introduced cervical screening it has been with the adoption of VIA [Visual Inspection with Acetic Acid] as VIA requires few tools (dilute white vinegar and the naked eye) to observe cervical abnormalities, allowing for same day cryotherapy or thermoablation. However, VIA is subjective, has low specificity, and does require training and ongoing quality assurance.

Observational studies [3], followed by randomised controlled trials (RCTs) [4–8], (largely performed in higher income countries) have consistently shown the superior performance of molecular nucleic acid testing [NAT] in detecting HPV DNA or RNA for cervical cancer screening, as these tests are more sensitive in predicting the development or detection of underlying lesions, as well as being more objective with less inter-operator variation. In higher HPV prevalence populations, such as immunocompromised women including women living with HIV (WLWH), NAT screening is suboptimal and requires biomarkers for dysplasia specificity. (See detail below under HPV NAT primary screening in LMIC) In general, a negative HPV test is associated with a substantially lower risk of cervical precancer and cancer over time than a negative cytology or negative VIA result.

3. International performance guidelines

In the pivotal RCTs, designed to assess the performance of HPV testing as a primary screen for cervical disease, the index assays used were Hybrid Capture II (HC2, Qiagen, Gaithersburg, MD, USA) or GP5+6+ PCR-EIA, which both detect DNA of 13 or 14 oncogenic or high-risk (hr) HPV genotypes [4–8]. The International Agency for Research on Cancer [IARC] has classified 12 HPV types as oncogenic for cervical cancer (16,18,31,33,35,39,45,51,52,56,58 and 59). These 12 types are categorised by IARC as group I carcinogens. Often hrHPV assays target two more types: HPV68 (classified as belonging to IARC group IIa, = *probably carcinogenic*) and HPV66 (group IIb = *possibly carcinogenic*). In addition, certain HPV tests target more *possibly carcinogenic* types (26, 53, 67, 70, 73, 82). These types can be found in some rare cases of cervical cancer. However, for cervical cancer screening, it is sufficient to target only the 12 oncogenic types (group I), since adding more types only marginally increases the sensitivity for precancerous lesions that may progress to cancer, but substantially decreases the clinical specificity [9]. Of note HPV16 and HPV18 carry the greatest oncogenic risk globally with HPV16 being the most oncogenic HPV. [9]. Based on international consensus, equivalency criteria were created through which other HPV NATs could be assessed in order to determine acceptance for use in cervical population screening [10]. These criteria, known as the Meijer criteria [10], incorporated metrics for non-inferior accuracy (clinical sensitivity and specificity) and intra- & inter-laboratory reproducibility to detect cervical intraepithelial neoplasia grade 2 and worse [CIN2+] lesions in screening samples compared to either of these two standard comparator tests. However, these criteria do not include the cumulative CIN3+ incidence rate after a negative test result (screening efficiency) which is critical for screening programs with extended intervals to avoid interval (pre) cancers.

It is noteworthy that a plethora of screening NAT tests exists. A 2012 review, identified 125 distinct assays and at least 84 variants, but with very few validated in clinical practice [11] or in adequately designed studies. Subsequently in 2015, a systematic review of screening and validation studies was performed and: this yielded a short subset of assays fulfilling the international criteria [12]. To address this paucity of validated assays, including those with genotyping capabilities, the VALGENT (VALidation of HPV GENotyping Tests) framework was created by Arbyn et al to help expedite the evaluation of HPV tests according to the Meijer 2009 criteria [13]. VALGENT is a robust protocol for validation and includes capacity for the assessment of HPV assays [13]. These validation frameworks have utilised cross-sectional and longitudinal design studies of clinician-collected cervical specimens.

A recently published updated review in 2020 revealed an almost doubling of distinct HPV assays, with 254 assays with 425 variants available on the global market: yet most had no analytical or clinical evaluation [14]. Furthermore, more than 90% had no regulatory evaluation, nor were evaluated following a stringent clinical validation protocol [14]. In April 2021, an updated list of HPV assays suitable for primary cervical cancer screening was published for guidance for countries choosing to use an HPV NAT assay [15]. (See Table 1 for sufficiently validated assays to use.) In addition, at the time of preparation of this document, three HPV assays have been through the WHO prequalification process [PQ] and it is likely this number will increase. WHO PQ is a process created to provide assurance as new *in vitro* diagnostic medical devices/ products enter the global market, with respect to their quality, safety and performance. For example, for products such as HPV NAT tests, PQ serves as a quality assurance mark for WHO Member States, UN agencies, and international procurers. The process for PQ includes the following: a review of the product dossier provided by the manufacturer (product description, risk analysis, analytical and clinical validation and verification studies, stability studies, etc.); an inspection of the manufacturing site(s); and an independent performance evaluation and labeling review. PQ assessment specifically focuses on relevant aspects for resource-limited settings [16].

A recent comprehensive overview by Cuschieri et al details quality-considerations and challenges, including assay and platform validation, internal quality control selection, infrastructure to prevent sample contamination and strengths and weaknesses of external quality assurance schemes [17]. In addition, generic guidance for quality monitoring and assurance of nucleic acid amplification tests (irrespective of target) can be helpful and some recent useful guidelines from 2010-2018 are referenced here [18–21].

Also strongly recommended is continuous monitoring of testing and participation in a real-time QC program, similar to programs used to monitor testing for other infectious agents. This is accomplished by laboratories testing an externally-sourced QC sample, which has reactivity close to the assay's lower cut-off or limit of detection with each

Table 1
List of HPV assays validated for cervical cancer screening as stand-alone test or in combination with cytology. Adapted from Arbyn et al CMI 2021 [15].

- Hybrid Capture 2 HPV DNA Test (Qiagen, Gaithersburg, MD, USA)
- GP5+/6+ PCR-EIA (Diassay, Rijkswijk, the Netherlands)
- Abbott RealTime High Risk HPV Test *** (Abbott Molecular, Des Plaines, IL, USA)
- Anyplex II HPV HR Detection (Seegene, Seoul, South Korea)
- BD Onclarity HPV Assay*(BD Diagnostics, Sparks, MD, USA)
- Cobas 4800 HPV Test* (Roche Molecular Diagnotics, Pleasanton, CA, USA)
- HPV-Risk Assay (Self-Screen BV, Amsterdam, The Netherlands)
- PapilloCheck HPV-Screening Test (Greiner Bio-One, Frickenhausen, Germany)
- Xpert HPV *** (Cepheid, Sunnyvale, CA, USA)
- Alinity m HR HPV Assay (Abbott Molecular, Des Plaines, IL, USA)
- Cobas 6800/8800 HPV Test* (Roche Molecular Diagnotics, Pleasanton, CA, USA)
- APTIMA HPV Assay ** (Hologic, Bedford, MA, USA)

* FDA approved for HPV alone primary screening
** FDA approved only with co-testing with cytology
*** WHO Prequalification of In Vitro Diagnostics
NB CareHPV™ ***Test is prequalified (2018), but not formally validated according to Meijer's criteria and/or VALGENT

test run and monitoring the test results of that sample over time to ensure consistency of performance. The results from a participating laboratory can be compared with those from other laboratories using the same assay and QC sample. This process provides real-time monitoring of assay analytical performance by the QC provider, and results that fall short of expected performance can be immediately investigated [22].

Apart from the use of validated assays, it is also important that all laboratory services themselves are accredited. Accredited requires that the laboratory needs to show evidence of its ability to correctly assess the content of blinded samples (proficiency testing panels). Another example of an EQA, is the international HPV DNA proficiency panel, traceable to International Standards, was assembled by the WHO HPV LabNet in 2007 and has been issued regularly ever since [23,24]. (See Table 2 for necessary measures of quality control when HPV NAT tests are performed in cervical cancer primary screening).

4. The future

With time and additional research, the role of extended genotyping over partial genotyping for HPV16/18 of those women found positive on screening will become evident [25]. In the future, addition of biomarkers of progression (for example host and/or viral methylation markers) will predict those with HPV 16/18 CIN2+ requiring treatment and reduce unnecessary treatment [26]. Clinical algorithms of care will therefore need continual review for modification, together with evaluation and endorsement by such bodies for example in the EU in updating the CE -IVD-R" mark. Moreover, based on data from South Africa, WLWH may benefit from a restricted genotype detection (to 8 genotypes) for cervical screening and potentially an altered threshold for positivity [27,28].

5. Sampling through self-collection

Most cervical screening programs do not reach the aim of 70% coverage and for some women and other persons with a cervix who do not identify as women, the lack of culturally appropriate facilities and/or providers often results in a decision to forego a reluctance to have a pelvic examination and screening. [29,30] Distance to reach a health care professional can also be an important barrier. Furthermore, many countries do not have the infrastructure or adequate personnel to have organized cytology screening programs. Validated HPV DNA assays based on NAT have similarly accuracy for CIN2/3+ on vaginal self-samples compared to cervical clinician-taken specimens [31]. As more cervical- screening programs are offering self-collected sampling in conjunction with NAT, particularly those who previously used VIA, this should reduce cultural, socio-economic and gender barriers to screening, and increase equity. The approach to self-sampling, whether as a universal offer or as way to engage a "hard to reach population" is likely to differ according to country-specific infrastructure and priorities. Nevertheless, before embedding self-sampling into any screening program, appropriate validation of the each component of the screening needs assessment and includes the collection and transport devices as well as the HPV assay combination, in the laboratory(s) that will be performing the testing routinely - is key, particularly as few test manufacturers – including many of those listed in Table 1 - have a formal claim for self-sampling at time of preparation of this document. To support this, a new validation protocol for emerging HPV tests is being developed which incorporates the contemporaneous collection of a self-sample as well as a clinician taken sample. The VALHUDES protocol generates evidence on tests with similar clinical accuracy on self-versus clinician-taken samples [32]. The principle is that if the HPV test validated on clinician collected samples has similar performance on self-collected samples, then the test can be used for screening self-collected samples. Moreover, for alternative self-collection devices for an already clinically validated combination test or device, analytical test concordance (self vs clinician collected) could be accepted as sufficient evidence [33].

Table 2
Recommended QC measures for HPV NAT cervical cancer screening tests.

Assay-specific:
– Including the 12 HR-HPV genotypes classified as carcinogenic (IARC group I)
– Not including more than 13 to 14 genotypes in total, if not a fully genotyping assay
– No additional HR-HPV that reduce the clinical specificity
– No low-risk HPV genotypes included
– Clinically validated assay or validated in comparison to standard comparator tests HCII or GP5+/6+ PCR
– Internal control for sample cellularity
– Positive control for assay performance
– Negative control for excluding contamination
– Approved as IVD by relevant approval bodies (e.g., FDA, CE, WHO)
Laboratory-specific
– Infrastructure to prevent sample contamination with post PCR products
– Participation in regular proficiency testing of external samples
– Monitoring of processes
– QC/QA management

6. HPV NAT primary screening in LMIC

The highest burden of cervical cancer is seen in countries with low financial resources, lack of screening activities, non-organized and non-quality-controlled programs, high prevalence of risk factors such as endemic HIV, and with high endemic HPV prevalence also at older ages. In the context of high HPV prevalence and insufficient resources for triage, HPV NAT testing can become problematic and needs adequate modification to ensure specificity. Reduction in the spectrum of types tested for to the eight most carcinogenic HPV types has been proposed [24]. The addition of biomarkers, such as cellular HPV-induced proteins or gene expression modifying promoter methylation tests, to the screening program may be necessary to identify women in true need of therapy and to avoid overwhelming the health care system [25,26].

7. Impact of COVID-19

The SARS-CoV-2 pandemic has overwhelmed hospitals limiting their capacity to perform routine gynaecological procedures. As patients with serious medical conditions that should undergo elective interventions generally do not have the same entitlement to acute care as COVID-19 patients, this one-sided prioritisation system may have life-threatening consequences, especially for affected patients diagnosed with CIN3 or with cervical cancer [34]. Lockdown measures affecting clinics, public transportation, and schools have severely compromised screening, vaccination and treatment efforts: catch-up programs should be planned and offered.

Although oncological operations or interventions in symptomatic patients have suffered during COVID-19 [35] office-based gynecologists and cervical cancer screening centers that carry the major burden of cervical screening have also reported that women attend at lower rates, as they fear acquiring COVID-19 through contact with other patients.

The SARS-CoV-2 pandemic thereby counteracts the worldwide efforts to reduce cases and mortality of cervical cancer. However, a silver lining of the COVID-19 pandemic has been the increased availability of molecular platforms and appropriate staff qualified in molecular technology in most countries due to the rapid scale up of COVID-19 testing: these can now also be deployed for HPV testing. Most countries have also built up a re-call system (for those who are COVID-19 positive) which can be utilized for managing those with positive HPV screening tests. It is noteworthy that in many countries, the idea of recalling patients was thought to be nearly impossible. Yet, COVID-19 has forced the strengthening of public health infrastructure with its effective recall system, the infrastructure which must be incorporated into cervical screening in the long term.

8. Education and addressing stigma

Switching from cytology to HPV testing is a major paradigm change. While it is important to consider the technical requirements along with QA and QC issues, professionals and programs must place equal emphasis on education and addressing the potential stigma associated with HPV testing. The majority of healthcare professionals and the public still focus on HPV as a sexually transmitted DISEASE (rather than an usually asymptomatic, transient and near universal infection for which we have effective prophylactic vaccines to prevent associated cancers) and this needs to be addressed if we are to achieve the 70% uptake among eligible women. To emphasise this point, the mucosal HPVs are largely (although not exclusively) transmitted by sexual contact (even intimate genital skin to genital skin) and are a very common infection, whereas the resultant diseases (clinical manifestations eg warts, precancerous lesions, cancer) are less so. Accordingly, with a reduction in infection from widespread vaccination, reductions in HPV-related diseases will occur. Scientific progress made in terms of technology must be matched with appropriate messaging/education for it to be accepted widely. Therefore, it is imperative that the narrative for primary HPV testing be standardized and agreed locally with tailoring to the local community as required.

9. Conclusion

Guidelines for cervical screening using NAT assays have recently been published by WHO [36] and in mid-2022 assessed the role for use of HPV mRNA detection as a primary screening test [37]. However, these guidelines, which support the use of HPV NAT detection in a screen, triage and treat or a screen and treat approach starting at the age of 30 years with regular screening every 5 to 10 years, recommend regulatory approved HPV assays. We await the next phase of the development of implementation guidelines for laboratories which will focus on choice of assays.

We emphasise that assays validated for clinical screening must be able to detect those with prevalent or incipient CIN3+ and are different to those adopted for surveillance (vaccine impact/effectiveness) which are of higher analytical sensitivity, detecting a lower quantity of HPV, not necessarily of clinical relevance. The cost of clinical screening assays needs to be affordable for all. Continuous and rigorous QA and QC checks are essential. In processing self-collected samples, amplification assays should be used. Although the COVID-19 pandemic has created several challenges including limited reagent availability, more laboratories are now equipped with the knowledge and rapid large-throughput instruments to ultimately use for HPV assays as a result of the pandemic. Although the pandemic has taught us how screening and vaccination programs can be compromised, it has also highlighted the importance of catch up and returning to routines.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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