Methodologies of Primary HPV Testing

Subjects: Others

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Definition

The human papillomavirus is one of the most common sexually transmitted viruses, and an infection from this virus may become persistent, leading to diseases such as cervical cancer. In the past, cytology-based methods such as the Papanicolaou (Pap) test were imperative to identify the disease at a stage where it can be treated. However, since the 1980s where the etiological association of HPV and cervical cancer was identified, new tests began emerging directed towards identifying the virus. Furthermore, as the biology of HPV along with the relationships with its host are elucidated, these tests and treatments further advance. Recently in Europe, there is a movement towards the implementation of HPV testing methodologies in national screening programs to precede cytological testing. These screening strategies are recommended by the European guidelines and the World Health Organization. This review presents the current HPV testing methodologies, their application in organized population-based cervical cancer screening programs based on the most recent European guidelines, and their implementation status in countries in Europe.

1. Cervical Cytology and Reasons That Lead to HPV-Based Approaches

Methods that are based on cytology such as the Pap test rely on the morphologic interpretation of cells collected from the woman's cervix in order to identify if there is any degree of cellular degeneration [1]. Cytology based testing has been the gold standard to test for cervical cancer since the development of the Pap test, primarily due to its high specificity; however, it is characterized by certain drawbacks. It has poor reproducibility, and it can be affected by blood and mucus obscuration, imperfect fixation, and non-uniform distribution of cells. These issues may hinder the already difficult interpretation of results; hence, highly trained personnel are required [2][3]. Furthermore, despite alternatives and efforts to improve upon methods relying on cytology, such as the UltraFast staining technique [4], liquid-based cytology (LBC) with the ThinPrep® Pap test (Hologic, Inc, Marlborough, MA, USA) and SurePathTM (SP; BD Diagnostics, Burlington, NC, USA) [3][5], and visual inspection by acetic acid or Lugol's iodine [6], the sensitivity is not optimal, yielding uncertain results, such as atypical squamous cells of undetermined significance (ASCUS, or ASC-US after the 2001 Bethesda Workshop). These results require close and constant follow up, which may lead to increased referrals for colposcopy and treatment [7].

2. Reasoning of HPV Testing Implementation in Screening Programs

HPV testing is a highly sensitive, objective molecular approach to screen for cervical cancer that does not rely on the morphologic interpretation of results, which in cytology may be subject to inter-observer variability [8]. HPV testing relies on the detection of the virus or effects of the viral infection to discover high-grade cervical dysplasia [9]. A benefit of HPV testing is that it allows for longer screening intervals due to fact that hrHPV requires a longer duration of time to progress to cancer than cells that are in the pre-cancer stage [10]. In fact, the European guidelines recommend that primary HPV testing may be performed at a five-year interval with the possibility to be extended to up to 10 years based on the medical history and age of the woman [11][12]. Furthermore, along with high clinical sensitivity and objectiveness, HPV testing also has a high negative predictive value (NPV), low training requirements, high reproducibility, and a high throughput capacity [13][14][15]. When taken together, and in conjunction with HPV vaccination, primary HPV testing every five years with cytology as a triage proved to be a more cost-effective option [16]. However, it is important to take in account the biology of the virus in relation to its host in order to decide the starting screening age. Thus, to account for the relatively lower specificity of the test and to avoid unnecessary follow-up or overtreatment of women likely having transient HPV

infections, the European guidelines recommend the starting age for primary HPV testing to be after the age of 30 and up to 35 [11][12]. Yet, in countries or regions where a primary cytology program is predominant and successful, the European recommendations allow the program to continue to run for the ages 20–30, while implementing primary HPV testing for ages above 30 [11][12]. Conversely, the age to exist a screening program is recommended to be 60–65, although women with a negative HPV screening history from the age of 55 are at low risk for an HPV infection that may become persistent and subsequently develop to cervical cancer [12][17]. Additionally, cytology testing has also been reported as suboptimal for women of this age range and for post-menopausal women due to epithelial atrophy and less accessible transformation zones, which are found in the cervical canal [18][19]. Nonetheless, since the risk still exists for that cohort, the age to stop screening with HPV testing is still under consideration, and it is continuously revised as scientific evidence is accumulated [18].

3. HPV Testing Assays and Validation

A concern of screening programs, particularly those based on HPV testing, stems from the fact that many viral targets (e.g., E6/E7 HPV mRNA, or L1, L2, E6/E7 HPV DNA, whole genome HPV DNA) may be used to detect an HPV infection. Due to this aspect of HPV testing, there is a plethora of tests available either in-house or commercial, yet only a number of them have been validated and approved for routine testing. Currently, there are 254 distinct commercial tests, and more than 425 variants of those tests have been identified [20]. These tests can be divided into hrHPV DNA, hrHPV with partial genotyping for the main hrHPVs, full HPV DNA genotyping tests, HPV DNA type/group-specific tests, hrHPV E6/E7 mRNA tests, in situ hybridization DNA in mRNA-based HPV tests, as well as tests identifying HPV DNA targeting miscellaneous HPV types [20]. These tests are based on the principles of Polymerase Chain Reaction (PCR) amplification coupled with sequencing, restriction fragment length polymorphism (RFLP) analysis, or hybridization assays. Additionally, other tests are based on real-time detection, transcription-mediated amplification (TMA) or nucleic-acid sequenced based amplification (NASBA) [21]. Namely, HPV tests that are currently circulating are Xpert HPV (Cepheid), PapilloCheck (Greiner Bio-One), INNO-LiPA HPV Genotyping Extra (Innogenetics), Cobas 6800/8800 HPV Test (Roche Molecular Systems Inc., Alameda, CA, USA), and HPV-Risk Assay (Self-screen BV, Amsterdam, Netherlands); hence, proper criteria (Meijer Criteria) and validation initiatives are required to ascertain which assays are appropriate for cervical cancer screening [20][22][23][24]. Specifically, an international expert committee in 2009 proposed criteria to denote assays suitable for cervical cancer screening [22][24]. These criteria aim to assure that candidate hrHPV tests should have an ideal balance between clinical specificity and sensitivity for the detection of CIN2/3, consequently reducing the number of follow up tests a woman has to undergo. For these purposes, new hrHPV DNA assays are compared to the Hybrid Capture 2 (HC2) or GP5+/6+ PCR- enzyme immunoassay (EIA) tests that are used as comparator tests due to their extensive clinical validation. Furthermore, each new test should be highly reproducible and applied to a clinically relevant set of samples characterized by various degrees of CIN from a screening cohort of women within the 30–60-year age group [22][24]. In this effort of a standardized validation, the international framework “Validation of HPV Genotyping Tests” (VALGENT) was launched in order to provide a comprehensive validation and comparison for HPV genotyping tests to be used for clinically relevant results, which is achieved through the employment of sample populations that are relevant for primary cervical cancer screening [25]. As of July 2019, there are 15 commercial HPV assays that are either completely or partially validated to be used for cervical cancer diagnostics based on primary HPV testing [25][26][27]. The list includes but is not limited to HC2, HPV DNA Test (Qiagen), cobas 4800 HPV Test (Roche), APTIMA HPV Assay (Hologic), and BD Onclarity HPV Assay (Becton Dickinson) [26]. In **Table 1**, a selection of HPV tests is presented that are used in primary HPV screening and triage testing, as well as tests used as comparator tests for validation purposes, indicating their technical characteristics, the category they are assigned to, their validation, and intended use [9][20][23][28][29][30][31][32][33][34][35][36][37][38].

Table 1. Selection of tests that use different targets and methodologies for HPV detection used in HPV screening as well as tests used as comparator tests for validation purposes.

Tests	Hybrid Capture 2 (Qiagen)	GP5+/6+ EIA [a]	Cobas 4800 HPV Test (Roche)	APTIMA HPV Assay (Hologic)	BD Onclarity HPV Assay
Type of assay	Signal amplification, hybrid capture	PCR, probe hybridization	Real-time PCR detection	Transcription mediated amplification, probe hybridization	Real-time PCR detection
Targets	DNA, Whole viral genome	L1 DNA, 150 bp	L1 DNA 200 bp	E6/E7 mRNA	E6 and E7 DNA
HPV Subtypes detected	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Individual genotyping for: 16, 18	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Reflex Partial genotyping for: 16, 18–45	33–58; 56–59–66; 35–39–68 [f]. Individual genotyping for: 16, 18, 31, 45, 51, and 52
Internal Controls Human genes	NO	NO	Internal human β-globin control	Internal RNA transcript (HPV16 E6/7) control	Internal human β-globin control
Capacity Batch size	88	96 samples in 9.5 h [e]	96	Panther system 100 and 250 test /Tigris DTS system 250	46
VALGENT Validation	Standard comparator tests for validation [b]	Standard comparator tests for validation [b]	YES	YES	YES
US FDA [c] Validation	YES	NO	YES	YES	YES
CE Mark [d] Validation	YES	YES	YES	YES	YES
Uses within a screening program	ASC-US Triage, test-of-cure	ASC-US Triage, test-of-cure	ASC-US Triage/co-testing/Primary testing	ASC-US Triage/co-testing	ASC-US Triage/co-testing/Primary testing

[a] GP5+/6+ enzyme immunoassay (EIA), DDL Diagnostic Laboratory (Rijswijk, The Netherlands). [b] HC2 and GP5+/6+ PCR-EIA are extensively clinically validated in randomised trials, used as standard comparator tests for HPV assay validation. [c] United States Food and Drug Administration. [d] European Commission CE (Conformité Européenne) marking. [e] For the GP5+/6+ enzyme immunoassay (EIA), the number of tests in the kit was reported along with the time required for results [29]. [f] The BD Onclarity HPV Assay genotypes eight genotypes in three groupings (HPV 33 and 58; HPV 56, 59, and 66; and HPV 35, 39, and 68).

4. Screening Algorithms Employing Primary HPV Testing

It is important to note that primary HPV testing is optimally part of a screening algorithm that employs triage and follow-up testing. This screening algorithm is imperative for the proper management of test results. Thus, with the expected increase in positive results from HPV testing, the European guidelines recommend cytology testing as a triage in order to avoid a large influx of referrals for colposcopy [12]. An HPV-based screening algorithm begins with the primary test as shown in **Figure 1**, where a positive HPV result moves further along the algorithm to secondary testing and cytology triage. In the case that the primary HPV test has genotyping capabilities and it is positive for HPV16 and HPV18, then it is acceptable for the woman to be directly referred for colposcopy, even without a cytology intermediate test [12]. If cytology triage testing shows a positive result then it is referred for colposcopy. A benefit of primary HPV

testing followed by cytology triage is that HPV negative results, which may have had the possibility to be ASC-US cases, would not be referred to and burden cytological testing, since they are essentially unlikely to pose the threat of pre-cancer or cancer [39]. Additionally, knowledge of the HPV status has been associated with an increase in the predictive value of the cytologist [15]. This still leaves the matter of HPV-positive, cytology-negative women (repeat testing in **Figure 1**) who are still at risk for having been identified with hrHPV. The European guidelines call for shorter intervals of repeat testing; however, evidence is still inconclusive to suggest one specific route [12]. For this reason, three possible routes are suggested for policy makers, where repeat testing may be performed through HPV testing, cytology, or HPV testing with cytology triage. Ultimately, positive results of hrHPV and abnormal cytology are referred to colposcopy (Decision, **Figure 1**) and in the case where high-grade cervical lesions are diagnosed, they are followed by treatments such as surgical excision, cryotherapy, and the loop electrosurgical excision procedure (LEEP) [40]. Despite the high success rate of these treatments, there is still a chance for residual or recurrent pre-cancer, and for this reason, HPV testing is also suggested for post treatment monitoring [41][42].

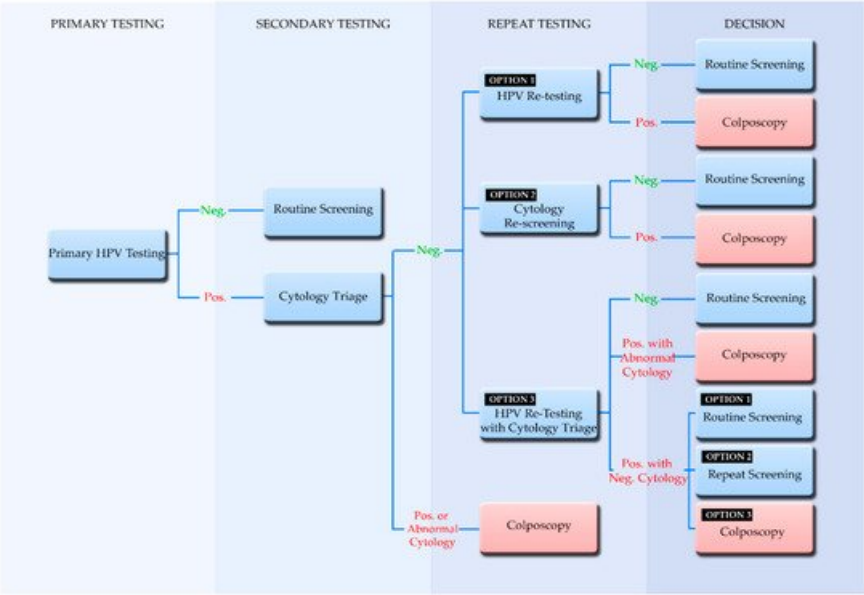

Figure 1. Management algorithm in primary HPV screening. Abnormal cytology refers to a borderline or more severe cytological result. This figure was adapted from Chrysostomou et al. (2018) [43]. This algorithm was developed based on "The supplements of the second edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening of 2015" [12].

5. Participation in Screening and the Implementation of Self-Sampling

In the implementation of any methodology in a screening program, participation is imperative for its success. In order to tackle this issue, which may be caused by women having difficulties in accessing health services, self-sampling is also considered as an option [44]. In this regard, it is also important to consider the attitude of women towards self-sampling. In a study by Leinonen et al. (2018), high acceptability and positive attitudes were observed towards self-sampling, with no differences in preference based on age, education, and marital status [45]. Additionally, even though women expressed more confidence in samples taken from trained personnel they would still prefer self-collection at home [45]. Yet, self-sampling can also be performed at a specialized facility, by the women themselves or with trained personnel assistance, thereby providing the option to ask questions and receive assurance that the sample was taken correctly [46]. Currently, kits for hrHPV self-sampling show great promise as means to increase participation in screening programs and they can achieve a higher degree of accuracy than those for cytology, reportedly having similar sensitivity and specificity to samples taken by trained medical personnel [44][45]. Importantly, in a meta-analysis study by Arbyn et al. (2018), hrHPV testing from self-sampling was shown to have comparable sensitivity to detect cervical intraepithelial neoplasia

(CIN2+) and CIN3+, with almost as much specificity in comparison to clinical samples [47]. Interestingly, PCR-based hrHPV testing from self-sampling was shown to have higher sensitivity and specificity (to exclude CIN2+) than signal amplification-based techniques, while mRNA testing and hrHPV DNA testing from self-sampling showed similar specificity but lower sensitivity than clinically collected samples [47].

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