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The Abbott RealTi*me* High Risk HPV test is a clinically validated human papillomavirus assay for triage in the referral population and use in primary cervical cancer screening in women 30 years and older: a review of validation studies

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Abstract

Introduction: Human papillomavirus (HPV) testing has become an essential part of current clinical practice in the management of cervical cancer and precancerous lesions. We reviewed the most important validation studies of a next-generation real-time polymerase chain reaction–based assay, the RealTi*me* High Risk HPV test (RealTi*me*)(Abbott Molecular, Des Plaines, IL, USA), for triage in referral population settings and for use in primary cervical cancer screening in women 30 years and older published in peer-reviewed journals from 2009 to 2013. RealTi*me* is designed to detect 14 high-risk HPV genotypes with concurrent distinction of HPV-16 and HPV-18 from 12 other HPV genotypes. The test was launched on the European market in January 2009 and is currently used in many laboratories worldwide for routine detection of HPV.

Methods: We concisely reviewed validation studies of a next-generation real-time polymerase chain reaction (PCR)–based assay: the Abbott RealTi*me* High Risk HPV test.

Results: Eight validation studies of RealTi*me* in referral settings showed its consistently high absolute clinical sensitivity for both CIN2+ (range 88.3–100%) and CIN3+ (range 93.0–100%), as well as comparative clinical sensitivity relative to the currently most widely used HPV test: the Qiagen/Digene Hybrid Capture 2 HPV DNA Test (HC2). Due to the significantly different composition of the referral populations, RealTi*me* absolute clinical specificity for CIN2+ and CIN3+ varied greatly across studies, but was comparable relative to HC2. Four validation studies of RealTi*me* performance in cervical cancer screening settings showed its consistently high absolute clinical sensitivity for both CIN2+ and CIN3+, as well as comparative clinical sensitivity and specificity relative to HC2 and GP5+/6+ PCR.

Conclusion: RealTi*me* has been extensively evaluated in the last 4 years. RealTi*me* can be considered clinically validated for triage in referral population settings and for use in primary cervical cancer screening in women 30 years and older.

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Introduction

Persistent infection with 10 to 15 genotypes of human papillomaviruses (HPV) known as high-risk HPV (hrHPV) is a necessary etiological factor in the development of cervical carcinoma. HPV-16 and HPV-18 together account for approximately 70% of cervical cancers worldwide (1). Consequently, in several countries (including Slovenia) hrHPV testing has become an invaluable part of clinical guidelines for cervical carcinoma screening, triage, and follow-up after treatment. The four major agreed-upon indications for HPV testing in current clinical practice are: 1) triage of women with equivocal cytology results showing the presence of atypical squamous cells of undetermined significance (ASC-US) in order to determine which patients should be referred for colposcopy; 2) follow-up of women with abnormal screening cytology results that are negative at initial colposcopy/biopsy; 3) prediction of the therapeutic outcome after treatment of CIN2+; and 4) primary screening of women 30 years and older in combination with a Pap smear to detect cervical cancer precursors (2–5). Another potential application of HPV testing is quality control of cervical cytology (6).

In a recent comprehensive inventory of commercial tests for detecting alpha-HPV, we identified at least 125 distinct HPV tests and at least 84 variants of the original tests (2). However, our study showed that only a small subset of HPV tests has documented clinical performance for any of the standard HPV testing indications. For more than 75% of HPV tests currently on the market, no single publication in peer-reviewed literature can be identified. We strongly recommended that HPV tests that have not been properly clinically validated and that lack proof of reliability, reproducibility, and accuracy should not be used in clinical management (2).

Here we present a concise review of validation studies of a next-generation real-time polymerase chain reaction (PCR)–based assay, the Abbott RealTi*me* High Risk HPV test (RealTi*me*) (Abbott Molecular, Des Plaines, IL, USA), for triage in referral population settings and for use in primary cervical cancer screening in women 30 years and older. RealTi*me* was launched on the European market in January 2009 and is currently used in many laboratories worldwide for routine detection of hrHPV. Together with the cobas® 4800 HPV Test (Roche Molecular Systems Inc., Alameda, CA, USA), RealTi*me* belongs to the group of next-generation real-time PCR-based HPV DNA assays in which detection of 14 HPV genotypes is combined with concurrent genotyping for HPV-16 and HPV-18 (2, 7). The design of such HPV tests was based on the results of clinical studies that demonstrated the exceptionally high oncogenic potential of HPV-16 and HPV-18 compared to other hrHPV types and showed that tests simultaneously

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distinguishing HPV genotypes HPV-16 and HPV-18 may identify women at greatest risk of CIN3+ and may permit less aggressive management of women with other hrHPV infections (8).

Description of the test

The Abbott RealTi*me* High Risk HPV test is a real-time PCR-based assay for concurrent detection and individual genotyping of HPV-16 and HPV-18 and pooled detection of 12 other hrHPV genotypes: HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66, and HPV-68. The HPV target sequence for RealTi*me* is located in the conserved L1 region of the genome. RealTi*me* is performed on the m2000rt real-time PCR instrument using a modified GP5+/6+ primer mix consisting of three forward primers and two reverse primers designed to hybridize to an approximately 150-base HPV consensus region (9). The internal process control (IC) designed for monitoring sample adequacy and DNA extraction and amplification target sequence is amplified using a primer set targeting a region of 136 bases in the human beta-globin gene. The HPV and internal control probes are single-stranded DNA oligonucleotides modified with a fluorescent moiety covalently linked to one end of the probe and a quenching moiety to the other end (9). Through the distinct labels, signals for HPV-16, HPV-18, non-HPV-16/18 types, and IC can be simultaneously detected and distinguished in a single reaction. The assay also has a proprietary algorithm for amplification curve validation.

The RealTi*me* turnaround time is 6 to 8 h for 96 samples, depending on the method used for DNA extraction. The fully automated high-throughput instrument m2000sp or the smaller m24sp instrument can be used for DNA extraction or, alternatively, DNA can be prepared manually. The assay is officially validated for use with cervical specimens collected with ThinPrep PreservCyt Solution, SurePath Preservative Fluid, and the Abbott CerviCollect Specimen Collection Kit; however, in our experience, cervical specimens collected in Digene Specimen Transport Media (STM) are also appropriate (10). In addition to cervical specimens, RealTi*me* can reliably detect and identify targeted HPVs in fresh tissue, fresh-frozen tissue, and tissue fixed with formalin and subsequently embedded in paraffin or paraplast (10–14).

Analytical validation studies

Probit analysis showed that the analytical sensitivity of RealTi*me* is between 500 and 5,000 copies of HPV DNA per assay, depending on the HPV type (9). An analytical specificity study on a panel of 41 bacteria, viruses, and fungi that can be found in the female anogenital tract revealed no cross-reactivity with any of the organisms tested, including all relevant low-risk HPV genotypes (9). The high analytical specificity of RealTi*me* and virtually no cross-reactivity with non-targeted HPV genotypes in clinical specimens has been confirmed in all studies performed to date, which have focused not only on the clinical performance of RealTi*me*, but also its analytical performance (10, 15–21).

Validation of RealTi*me* sensitivity for CIN3 and cervical cancer

The clinical sensitivity of the RealTi*me* test was initially evaluated in 593 archived cervical specimens from Amsterdam (the Netherlands) and the presence of hrHPV was detected in 97.2% (246/253) and 98.5% (335/340) of CIN3 and cervical cancer specimens, respectively (22). Of 12 hrHPV-negative specimens evaluated further, eight had invalid beta-globin results by the Roche Linear Array HPV Genotyping Test and four contained only low-risk HPVs. In a Slovenian study, HPV was detected by RealTi*me* in 96.4% (245/254) and 98.8% (84/85) of cases of CIN3 and cervical cancer containing targeted hrHPVs, respectively (23). As described below, the high sensitivity of RealTi*me* for CIN3+ lesions, including cervical cancer, has been confirmed in further RealTi*me* validation studies in the referral population and primary cervical cancer screening settings.

Clinical validation of RealTi*me* in a referral population setting

RealTi*me* clinical performance in a referral population setting has been evaluated in several studies (17–19, 24–28). The results of the most important studies with clinical endpoints (CIN2+ and/or CIN3+) are presented in Table 1. Although these eight studies differed significantly in the composition of the referral population for colposcopy (the majority enrolling women with abnormal cytology of any grade), the absolute clinical sensitivity of RealTi*me*, as well as its sensitivity relative to the clinically validated comparator test Hybrid Capture® 2 HPV DNA Test (HC2) (Qiagen, Hilden, Germany), were consistently high for both CIN2+ and CIN3+ in all studies performed to date (Table 1). As expected, the absolute clinical specificity for CIN2+/CIN3+ varied greatly across studies due to the heterogeneous nature of the referral populations (Table 1). However, the clinical specificity of RealTi*me* relative to HC2 was above 1.00 in all except one study (Table 1). RealTi*me* also performed well in both multi-HPV assay comparison studies: Predictors 1 (25) and Predictors 2 (28) were among the HPV assays with high clinical sensitivity for cervical high-grade disease and showed comparable clinical specificity with a few other clinically validated HPV DNA assays (25, 28, 29). The high clinical sensitivity and acceptable clinical specificity of RealTi*me* in the referral population was further confirmed in a recent meta-analysis (5).

Clinical validation of RealTi*me* for use in primary cervical cancer screening in women 30 years and older

RealTi*me* has been clinically validated for use in primary cervical cancer and pre-cancer screening in women 30 years and older in four studies (Table 2) (15, 16, 30, 31). A Slovenian study evaluated RealTi*me* prospectively in comparison with HC2 on 3,129 women (15). Italian (16) and Dutch (30) studies evaluated RealTi*me* following the "Guidelines for HPV DNA test requirements for primary cervical cancer screening in women 30 years and older" (32) in comparison with HC2 and GP5+/6+ PCR on retrospective samples collected from 998 and 927 women, respectively. As shown in Table 3, all three studies showed that RealTi*me* fulfilled the cross-sectional clinical equivalence criteria of the international consensus guidelines (32), which indicates that RealTi*me* can be considered a clinically validated assay for cervical cancer screening purposes. RealTi*me* also performed well in a multi-HPV assay comparison study (Predictors 3), being among HPV assays with the highest clinical sensitivity for cervical high-grade disease in women 30 years and older and showing comparable clinical specificity with other clinically validated HPV DNA assays (31). This was further confirmed in a recent meta-analysis (5), in which RealTi*me* was listed as one of four currently available HPV assays that can be considered clinically validated for use in primary screening.

Table 1 | **Absolute and relative clinical sensitivity and clinical specificity of the Abbott RealTime High Risk HPV test for CIN2+ and CIN3+ lesions (with 95% confidence intervals when available) established in eight studies that evaluated RealTime performance in referral settings. Relative clinical sensitivity and clinical specificity are calculated in comparison to performance characteristics of the clinically validated test HC2: RealTime values below 1.00 favor the comparator, and values above 1.00 favor RealTime.**

		CIN2+				CIN3+			
Study (reference)	Number of women	RealTime absolute sensitivity (95% CI)	RealTime relative sensitivity	RealTime absolute specificity (95% CI)	RealTime relative specificity	RealTime absolute sensitivity (95% CI)	RealTime relative sensitivity	RealTime absolute specificity (95% CI)	RealTime relative specificity
Huang S et al. (24)	702	97.8% (95.0–99.3)	1.02	32.8% (28.6–37.2)	0.92	100.0% (96.4–100.0)	1.02	26.6% (23.1–30.3)	0.91
Halfon P et al. (17)	143	90.0% (85–96)	0.95	50.0% (41–59)	1.00	NA	NA	NA	NA
Cuzick J et al. (25)	858	97.7% (NA)	0.98	31.5% (NA)	1.11	98.9% (NA)	0.99	34.7% (NA)	1.36
Halfon P et al. (26)	107	89.0% (79–99)	0.95	51.0% (39–63)	1.06	NA	NA	NA	NA
Wong OG et al. (27)	82	100.0% (NA)	1.00	20.8% (NA)	1.66	NA	NA	NA	NA
Venturoli S et al. (18)	412	88.3% (NA)	1.02	NA	NA	93.0% (88.1–98.0)	1.02	NA	NA
Szarewski A et al. (28)	1,099	93.3% (90.1–95.6)	0.97	27.3% (24.1–30.7)	1.40	97.3 (94.2–99.0)	0.96	NA	NA
Jentschke M et al. (19)	319	92.4% (87.0–96.0)	1.01	61.7% (53.8–69.2)	1.05	97.5% (NA)	1.04	NA	NA

Table 2 | **Absolute and relative clinical sensitivity and clinical specificity of the Abbott RealTime High Risk HPV test for CIN2+ lesions (with 95% confidence intervals when available) established in four studies that evaluated RealTime performance in primary cervical cancer screening settings in women 30 years and older. Relative clinical sensitivity and clinical specificity are calculated in comparison to performance characteristics of the clinically validated tests HC2 or GP5+/6+ PCR. RealTime values below 1.00 favor the comparator, and values above 1.00 favor RealTime.**

Study (reference)	Study type/ Specimen type	Number of cases (≥ CIN2)	Number of controls (< CIN2)	RealTime absolute sensitivity (95% CI)	RealTime absolute specificity (95% CI)	Reference HPV assay	Reference absolute sensitivity (95% CI)	Reference absolute specificity (95% CI)	RealTime relative sensitivity	RealTime relative specificity	Non inferiority test p-sensitivity p-specificity
Carozzi FM et al. (16)	retrospective, STM	84	914	96.4% (89.9–99.3)	92.3% (90.4–94.0)	HC2	97.6% (91.7–99.7)	92.6% (90.7–94.2)	0.99	1.00	p = 0.004 p = 0.008
Poljak M et al. (15)	prospective, PreservCyt	38	3,091	100.0% (86.5–100.0)	93.3% (92.4–94.2)	HC2	97.4% (86.2–99.9)	91.8% (90.8–92.7)	1.03	1.02	p = 0.004 p = 0.0003
Hesselink AT et al. (30)	retrospective, PreservCyt	68	859	95.6% (87.2–98.6)	92.0% (90.0–93.5)	GP5+/6+ PCR	98.5% (90.3–99.8)	91.8% (89.9–93.4)	0.97	1.00	p = 0.009 p = 0.0003
Cuzick J et al. (31)	retrospective, PreservCyt	16	4,629	100.0% (79.4–100.0)	90.3% (89.4–91.1)	HC2	100.0% (79.4–100.0)	88.8% (87.9–89.7)	1.00	1.02	NA

Table 3 | **Validation of intra-laboratory reproducibility and inter-laboratory agreement of the Abbott RealTi*me* High Risk HPV test.**

Study (reference)	Type of study	Number of samples	RealTi*me* overall reproducibility (95% CI)	Kappa (95% CI)
Carozzi FM et al. (16)	Intra-laboratory reproducibility	521	98.5% (97–99)	0.97 (0.95–0.99)
Poljak M et al. (15)	Intra-laboratory reproducibility	500	100.0% (99–100)	1.00 (0.90–1.00)
Poljak M et al. (15)	Inter-laboratory agreement (first round)	500	100.0% (99–100)	1.00 (0.98–1.00)
Poljak M et al. (15)	Inter-laboratory agreement (second round)	500	99.8% (98.7–99.9)	0.99 (0.98–1.00)
Hesselink AT et al. (30)	Intra-laboratory reproducibility	504	98.4% (97.2–99.2)	0.96
Hesselink AT et al. (30)	Inter-laboratory agreement	500	99.8% (99.1–99.9)	0.99

Validation of RealTi*me* intra-laboratory reproducibility and inter-laboratory agreement

Intra-laboratory reproducibility and inter-laboratory agreement of RealTi*me* have been extensively validated following the "Guidelines for HPV DNA test requirements for primary cervical cancer screening in women 30 years and older" (32) in three and two studies, respectively (15, 16, 30). As shown in Table 3, both intra-laboratory reproducibility and inter-laboratory agreement of RealTi*me* were well above confidence levels in all studies (> 87%, with kappa values > 0.5), confirming the exceptional reproducibility and reliability of RealTi*me* for detecting targeted hrHPV, even in samples stored for more than 3 years.

Conclusions

RealTi*me* has been extensively evaluated in the last 4 years and can be considered clinically validated for triage in referral population settings and for use in primary cervical cancer screening in women 30 years and older.

Disclosures

The Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana has received research funding from Abbott Molecular. Mario Poljak has received travel grants and honoraria from Abbott Molecular for speaking and for participating in conferences and sitting on an advisory board.

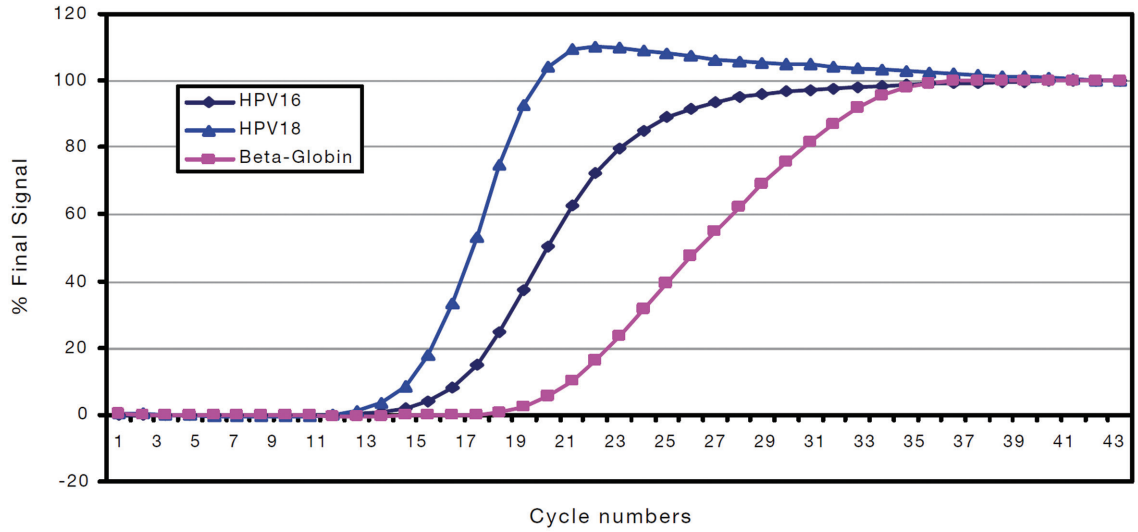

Figure 1 | Example of an Abbott RealTi*me* High Risk HPV test result in a cervical sample in which both HPV-16 and HPV-18 were detected. The assay uses four channels for detecting fluorescent signals: one for detecting an internal process control for sample adequacy and DNA extraction and amplification, a second for detecting HPV-16, a third for detecting HPV-18, and a fourth for aggregate detection of the 12 HPV types. A positive result for HPV-16 is visible as dark blue curve (positive in cycle number 14.37) and a positive result for HPV-18 as a pale blue curve (positive in cycle number 13.45). Internal process control based on amplification of the housekeeping beta-globin gene gave a positive signal in cycle number 19.51 (purple curve). The result for the aggregate detection of the 12 HPV types is negative (no specific curve present).

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