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Comparison of Human Papillomavirus Detection by Aptima HPV and cobas HPV Tests in a Population of Women Referred for Colposcopy following Detection of Atypical Squamous Cells of Undetermined Significance by Pap Cytology

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Few studies have compared the cobas HPV test to the Aptima HPV assay (AHPV) and the Aptima HPV 16 18/45 genotype assay (AHPV GT) for high-risk human papillomavirus (hrHPV) detection, clinical performance in detecting cervical intraepithelial neoplasia grade 2 (CIN2) or more severe (CIN2+) diagnoses, and risk stratification by partial HPV genotyping. The cobas HPV test is a DNA test that separately and concurrently detects HPV16, HPV18, and a pool of 12 other hrHPV types. AHPV is an RNA test for a pool of 14 hrHPV genotypes, and AHPV GT is an RNA test run on AHPV-positive results to detect HPV16 separately from HPV18 and HPV45, which are detected together. In a population of patients ($n = 988$) referred for colposcopy because of a cervical Pap cytology result of atypical squamous cells of undetermined significance (ASC-US), a cervical scrape specimen was taken, placed into a ThinPrep Pap test vial containing PreservCyt liquid cytology medium, and tested in a blinded fashion with cobas and AHPV and with AHPV GT for AHPV-positive results. The final diagnoses were based on a consensus panel review of the biopsy specimen histology. AHPV and cobas were equally sensitive for CIN2+ diagnoses (89.4% each; $P = 1.000$), and AHPV was more specific than cobas (63.1% versus 59.3%; $P \leq 0.001$). The percent total agreement, percent positive agreement, and kappa value were 90.9%, 81.1%, and 0.815, respectively. Risk stratification using partial HPV genotyping was similar for the two assays. AHPV and AHPV GT had similar sensitivity and risk stratification to cobas HPV, but they were more specific than cobas HPV.

High-risk human papillomavirus (hrHPV) testing has now been recommended for use in routine cervical cancer screening (1), to triage women with atypical squamous cells of undetermined significance (ASC-US) as a Pap result, and in surveillance follow-up of women after colposcopy or treatment (2). Three of the four U.S. Food and Drug Administration (FDA)-approved hrHPV tests (cobas HPV test [cobas; Roche, Pleasanton, CA], Hybrid Capture 2 [HC2; Qiagen, Gaithersburg, MD], and Cervista [Hologic, Bedford, MA]) qualitatively detect viral DNA sequences. The fourth U.S. FDA-approved hrHPV test, Aptima HPV assay (AHPV; Hologic), is a qualitative test for detecting mRNA expressed from viral E6/E7 oncogenes. While cobas offers concurrent partial genotyping for HPV16 and HPV18 with the detection of a pool of 12 other hrHPV genotypes, AHPV provides testing of a pool of these 14 hrHPV genotypes with a separate test (AHPV GT) available for partial genotyping of hrHPV-positive results for differentiation of HPV16 and HPV18/45 (with HPV18 and HPV45 detected together). Cervista also offers partial HPV genotyping for HPV16 alone and HPV18 alone. HPV16 and HPV18 detection have been recommended for the management of women with hrHPV-positive/Pap-negative results (1). Here, we present a head-to-head comparison of AHPV and cobas for the detection of hrHPV, for clinical performance in identifying women with cervical precancer, and for risk stratification by partial HPV genotyping in a population referred for colposcopy because of an ASC-US Pap result.

MATERIALS AND METHODS

Study procedures. Women who participated in this study were part of the CLEAR (clinical evaluation of Aptima mRNA) study, a pivotal, prospective, multicenter U.S. clinical study for the triage of women ages 30 years and older with normal Pap cytology and for women ages 21 years and older with ASC-US Pap cytology for colposcopy referral (3). The CLEAR study protocol was approved by institutional review boards at the participating centers, and the study was conducted in accordance with applicable regulatory requirements and good clinical practices. Informed consent was obtained prior to enrollment of the subjects. Women ages 21 years or older who were undergoing routine Pap testing and who had an ASC-US cytology result were invited to participate in the ASC-US arm of CLEAR. Women were recruited from 19 U.S. family planning and obstetric/gynecologic clinics (private and academic), family practice medical groups, and clinical research centers encompassing a wide geographic area representative of the U.S. population.

In addition to the ThinPrep specimen obtained at the introductory (baseline) visit, a ThinPrep specimen was also collected from the 988

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TABLE 1 hrHPV detection by cobas HPV and AHPV tests overall and stratified by diagnosis[a]

CIN grade[b]	AHPV$^+$	cobas$^+$	AHPV$^+$/ cobas$^+$	AHPV$^+$/ cobas$^-$	AHPV$^-$/ cobas$^+$	AHPV$^-$/ cobas$^-$	Total no. of cases	% Agreement	% Positive agreement	Kappa	*P*
All								90.9	81.1	0.815	0.0004
No. of cases	414	448	386	28	62	512	988				
% row	41.9	45.3	39.1	2.8	6.3	51.8					
CIN3+[c]								92.9	92.7	0.364	1
No. of cases	40	39	38	2	1	1	42				
% row	95.2	92.9	90.5	4.8	2.4	2.4					
CIN2								94.2	93.5	0.767	1
No. of cases	44	45	43	1	2	6	52				
% row	84.6	86.5	82.7	1.9	3.8	11.5					
<CIN2								90.6	78.4	0.803	0.0003
No. of cases	330	364	305	25	59	505	894				
% row	36.9	40.7	34.1	2.8	6.6	56.5					

[a] Paired results: positive (+) or negative (−); agreement statistics: percent agreement, percent positive agreement, and kappa value. hrHPV, high-risk human papillomavirus; AHPV, Aptima HPV. Differences in percent positive were tested for statistical significance using an exact version of the McNemar chi-square test.
[b] CIN3+, cervical intraepithelial neoplasia grade 3 or worse; CIN2, cervical intraepithelial neoplasia grade 2; % row, row percentage.
[c] Includes one case of adenocarcinoma *in situ*.

women sent to colposcopy due to an ASC-US cervical cytology result. The mean, median, and range of time between the baseline screening visit and the colposcopic referral were 33.7 days, 29 days, and 7 to 275 days, respectively. The ThinPrep specimen collected at colposcopy was sent to Hologic for aliquoting. Samples were stored for up to 21 months at 4°C before aliquots were made in the following order: (i) 4 ml neat, frozen at −70°C; (ii) 2 ml neat into 2 ml Aptima urine transport medium (Hologic), frozen at −70°C; (iii) 1 ml neat, frozen at −70°C; (iv) 2 ml neat, frozen at −70°C; and (v) remaining volume diluted 1:2.9 (the same ratio used in routine AHPV testing) in the Aptima specimen transport medium (Hologic), and 4-ml aliquots prepared and frozen at −70°C. One of these frozen 4-ml aliquots was used for AHPV and AHPV-GT testing (0.4 ml for each), and the 2-ml neat ThinPrep aliquot was used for cobas testing.

An endocervical curettage specimen and a punch biopsy specimen from each of 4 quadrants (by directed biopsy if lesions were visible, by random biopsy if no lesion was visible) were obtained from each subject in the study. Slides were prepared, stained with hematoxylin and eosin, and reviewed by up to 3 expert pathologists, and the consensus diagnosis was used for determining the disease status.

hrHPV testing. AHPV and AHPV GT testing were performed at Hologic according to the manufacturer's instructions using the Tigris DTS system. cobas testing using the cobas 4800 system was performed at the Laboratory Corporation of America (Burlington, NC) according to the manufacturer's instructions. All test operators were naive to each subject's previous test results and histology diagnosis. A specimen was considered test positive for hrHPV by cobas if any of the three cobas channels (HPV16, HPV18, or other 12 hrHPV types) was positive.

Further testing was performed on the baseline ThinPrep specimen with a validated reverse transcription-PCR (RT-PCR) sequencing assay for E6/E7 mRNA from 14 hrHPV types as previously described (4), with linear array (LA; Roche), and with HC2. Results from these baseline tests are presented for cases of CIN2+ diagnosis, in which testing of the specimen collected at colposcopy was negative by cobas, AHPV, or both tests.

Statistical analyses. For pairwise comparisons of AHPV and cobas for hrHPV testing and HPV risk groups, percent agreements, percent positive agreements, and/or kappa values were calculated for the entire population and stratified by the final panel review diagnosis (CIN3+, CIN2, and <CIN2). An exact version of the McNemar or symmetry test was used to test for differences in positivity for hrHPV detection or HPV risk groups, respectively.

Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and 95% confidence intervals (95% CI) for CIN2+ and CIN3+ diagnoses were calculated for both tests. An exact version of the McNemar or symmetry test was used to test for differences in predictive values and for differences in sensitivity and specificity, according to the method of Leisening and Pepe (5).

To evaluate the impact of detection of HPV45 by the AHPV GT assay, the odds ratios (OR) and 95% CIs were calculated among those subjects who were HPV18/45 positive by AHPV GT and HPV18 negative by cobas compared to those who were HPV18/45 positive by AHPV GT and HPV18 positive by cobas, using as a reference the HPV genotype result from LA testing of the baseline specimen.

Stata version 12.1 (Stata Corp., College Station, TX, USA) was used for most analyses; R version 3 (http://www.r-project.org/), using the package DTComPair, was used to test for statistical differences in predictive values. A P value of < 0.05 was considered statistically significant.

RESULTS

Table 1 shows the paired results of AHPV and cobas for hrHPV detection. In this colposcopy referral population, cobas was more likely than AHPV to test positive for any hrHPV (45.3% versus 41.9%; $P = 0.0004$). The percent total agreement, percent positive agreement, and kappa value were 90.9%, 81.1%, and 0.815, respectively. The percentages of tests that were hrHPV positive by AHPV and cobas were 95.2% and 92.9%, respectively, for women with CIN3+, 84.6% and 86.5%, respectively, for women with CIN2, and 36.9% and 40.7%, respectively, for women with <CIN2. cobas was more likely than AHPV to test positive among women with <CIN2 ($P = 0.0003$).

AHPV was 89.4% sensitive (95% CI, 81.3% to 94.8%) and 63.1% specific (95% CI, 59.8% to 66.3%), while cobas was 89.4% sensitive (95% CI, 81.3% to 94.8%) and 59.3% specific (95% CI, 56.0% to 62.5%), for CIN2+ ($n = 94$) (Table 2). AHPV was 95.2% sensitive (95% CI, 83.8% to 99.4%) and 60.5% specific (95% CI, 57.3% to 63.6%), while cobas was 92.9% sensitive (95% CI, 80.5% to 98.5%) and 56.8% specific (95% CI, 53.5% to 59.9%), for CIN3+ ($n = 42$). AHPV had a higher PPV than cobas for CIN2+ (20.3% versus 18.8%; $P = 0.01$) and CIN3+ (9.7% versus 8.7%; $P = 0.03$). There were no significant differences in the NPV.

TABLE 2 Sensitivity, specificity, PPV, and NPV with 95% CIs for diagnoses of CIN2+ and CIN3 for hrHPV detection by cobas HPV and AHPV tests[a]

Value type by CIN grade	AHPV		Cobas		
	Value (%)	95% CI (%)	Value (%)	95% CI (%)	*P*
CIN2+[b]					
Sensitivity	89.4	81.3–94.8	89.4	81.3–94.8	1
Specificity	63.1	59.8–66.3	59.3	56.0–62.5	0.0003
PPV	20.3	16.5–24.5	18.8	15.2–22.7	0.01
NPV	98.30	96.80–99.20	98.10	96.60–99.10	0.8
CIN3+[b]					
Sensitivity	95.2	83.8–99.4	92.9	80.5–98.5	1
Specificity	60.5	57.3–63.6	56.8	53.5–59.9	0.0002
PPV	9.7	7.0–12.9	8.7	6.3–11.7	0.03
NPV	99.70	98.70–100	99.40	98.40–99.90	0.5

[a] PPV, positive predictive value; NPV, negative predictive value; CIN2+, cervical intraepithelial grade 2 or more; CIN3, cervical intraepithelial grade 3; hrHPV, high-risk human papillomavirus; AHPV, Aptima HPV. Differences in sensitivity and specificity were tested for statistical significance using an exact version of the McNemar chi-square test.
[b] Includes one case of adenocarcinoma *in situ*.

The cases of CIN2+ in which AHPV and/or cobas tested negative are shown in Table 3. All three cases of AHPV-positive/cobas-negative results were also positive for hrHPV by HC2 and/or LA, suggesting that the cobas results were false negative. Two of the three cases were also positive for hrHPV E6/E7 mRNA by RT-PCR sequencing (and the third case had no result available for RT-PCR sequencing). All three cases of AHPV-negative/cobas-positive results were also positive for hrHPV by HC2 and/or LA, suggesting that the AHPV results were false negative. All three of these cases were negative for hrHPV E6/E7 mRNA by RT-PCR sequencing. The interpretation of the AHPV and cobas dual-negative results was less certain. Four of the 7 cases of CIN2+ were negative by HC2 but positive by LA for borderline hrHPV types, suggesting that they were either truly negative for disease, i.e., misclassified diagnoses of CIN2/3, or that the CIN2/3 lesions were the result of infections with untargeted HPV genotypes. The case of CIN3 diagnosed by the panel and by the community pathology reviews is most likely an example of a lesion that resulted from infection with untargeted genotypes. One case of CIN2 was positive by HC2 for borderline hrHPV types HPV53 and HPV61, suggesting that the lesion was due to an HPV infection not targeted by either of the screening assays. The last two of these seven cases were negative for HPV by all tests, suggesting that they were mostly likely truly negative, i.e., cases of misclassified diagnoses of CIN2. All seven AHPV and cobas dual-negative cases were negative for hrHPV E6/E7 mRNA by RNA sequencing.

Finally, we compared the detection of HPV16 and HPV18/45 by AHPV GT (among AHPV positives) versus HPV16 and HPV18 detection by cobas (Table 4). The results are shown hierarchically according to cancer risk: HPV16 positive; else HPV16 negative and HPV18 or HPV18/45 positive; else HPV16 and HPV18 or HPV16 and HPV18/45 negative but positive for the other hrHPV types; else hrHPV negative. HPV16 detection identified approximately 40% of CIN2+ and 50% of CIN3+ diagnoses by both assays (data not shown). cobas was more likely to categorize women as higher risk for disease due to the higher overall detection rate for HPV16 among all subjects ($P < 0.0001$). There was no

TABLE 3 Corresponding clinical and ancillary HPV testing of the consensus histology cases of CIN2 and CIN3 in which hrHPV detection by cobas HPV and/or AHPV tests was negative

Paired test result	Patient age (yr)	Histology by:		Clinical test result by:		Ancillary test HPV type result by[a]:			Test result interpretation[b]
		Consensus	Community	Cobas HPV	AHPV	HC2	E6/E7 RNA sequencing (HPV RNA genotype)	Linear array	
AHPV$^+$/cobas$^-$	29	CIN2	CIN1	−	+	+	58	33, 54, 58	False negative (cobas)
	37	CIN3	CIN3	−	+	−	18	18, 54	False negative (cobas)
	32	CIN3	CIN2	−	+	+	NA	82	False negative (cobas)[d] or untargeted
AHPV$^-$/cobas$^+$	22	CIN3	CIN3	+ (other)	−	NA	−	39, 45	False negative (AHPV)
	24	CIN2	CIN2	+ (HPV18)	−	+	−	6, 61	False negative (AHPV)[c] or untargeted
	28	CIN2	CIN2	+ (other)	−	+	−	52	False negative (AHPV)
AHPV$^-$/cobas$^-$	20	CIN2	CIN1	−	−	−	−	70	True negative[d] or untargeted[e]
	22	CIN2	CIN1	−	−	−	−	53	True negative[d] or untargeted[e]
	39	CIN2	Normal	−	−	−	−	61	True negative[d] or untargeted[e]
	30	CIN3	CIN3	−	−	−	−	82	True negative[d] or untargeted[e]
	23	CIN2	CIN1	−	−	+	−	53, 61	True negative[d] or untargeted[e]
	26	CIN2	CIN1	−	−	−	−	−	True negative[d]
	48	CIN2	CIN1	−	−	−	−	−	True negative[d]

[a] Conducted on the baseline specimen, not the specimen collected at colposcopy; NA, not available.
[b] Compared to histology diagnosis.
[c] Lesion caused by HPV genotypes not targeted by cobas or AHPV but detected via cross-reactivity by one of the tests.
[d] CIN2/3 that may be a misclassified diagnosis.
[e] Lesion caused by HPV genotypes not targeted by cobas or AHPV.

TABLE 4 Comparison of hrHPV and HPV genotype detection results, ranked hierarchically according to cancer risk, by cobas HPV and AHPV tests[a]

AHPV result by type and oncogenic risk	cobas result by HPV type				
	HPV16 positive	HPV18 positive	Other 12 hrHPV positive	hrHPV negative	Total
HPV16 positive					
No.	89	1	2	0	92
% of total	9.0	0.1	0.2	0.0	9.3
No. CIN2+	36	0	1	0	37
% CIN2+	38.3	0.0	1.1	0.0	39.4
HPV18/45 positive					
No.	1	32	18	1	52
% of total	0.1	3.2	1.8	0.1	5.3
No. CIN2+	1	8	2	1	12
% CIN2+	1.1	8.5	2.1	1.1	12.8
Other 11 hrHPV positive					
No.	12	3	228	27	270
% of total	1.2	0.3	23.1	2.7	27.3
No. CIN2+	3	0	30	2	35
% CIN2+	3.2	0.0	31.9	2.1	37.2
hrHPV negative					
No.	11	7	44	512	574
% of total	1.1	0.7	4.5	51.8	58.1
No. CIN2+	0	1	2	7	10
% CIN2+	0.0	1.1	2.1	7.4	10.6
Total					
No.	113	43	292	540	988
% of total	11.4	4.4	29.6	54.7	100.0
No. CIN2+	40	9	35	10	94
% CIN2+	42.6	9.6	37.2	10.6	100.0

[a] cobas separately detects HPV16 and HPV18 individually and concurrently with detection of a pool of 12 other hrHPV genotypes. AHPV GT separately detects HPV16 individually and HPV18 and HPV45 (HPV18/45) as a pool sequentially following positive testing for pool of 14 hrHPV genotypes. Presented is the number positive and percent of total samples tested positive of each paired result, and the number and the percentage of cervical intraepithelial neoplasia grade 2 or more severe diagnoses (CIN2+).

difference in the distribution of risk groups between tests for women diagnosed with CIN2+ ($P = 0.7$) (data not shown). Despite the differences in which group HPV45 was detected, the kappa value for the agreement between cobas and combined AHPV and AHPV GT was 0.782 (data not shown).

The OR was 96 (95% CI, 7.7 to 4,200) (data not shown) for detection of HPV45 (84.2%) versus HPV18 (5.3%) by LA on the baseline specimen among women who tested HPV18/45 positive by AHPV GT and HPV18 negative by cobas. By comparison, the OR was 0.0085 (95% CI, 0.00080 to 0.067) for HPV45 (6.9%) versus HPV18 (90.0%) by LA on the baseline specimen among women who tested HPV18/45 positive by AHPV GT and HPV18 positive by cobas.

DISCUSSION

In a study population of women referred for colposcopy because of an ASC-US Pap result, we found that AHPV and cobas were similarly sensitive and that AHPV was slightly more specific than cobas for CIN2+ and CIN3+, a result which has been reported previously for colposcopic referral populations using cytologic interpretations of mild or more severe dyskaryosis or using three consecutive interpretations of borderline dyskaryosis (6); using cytology diagnosis of ASC-US, low-grade squamous intraepithelial lesion (LSIL), or worse (7); and in a screening population (8). The two assay systems achieve comparable risk stratification for patient management using HPV genotyping, with only minor differences. For all subjects tested, HPV16 detection by cobas identified nonsignificantly more cases of CIN2+ than AHPV GT; 3 CIN2 cases were positive by cobas for HPV16 and were AHPV positive but were AHPV GT negative, although one of these cases was typed as HPV31 and HPV53 by LA. However, cobas was also more likely than AHPV GT to test positive for HPV16 among women with normal or CIN1 biopsy specimen results; 73 subjects were HPV16 positive by cobas versus 55 subjects who were HPV16 positive by AHPV GT in this disease-negative group. The inference from these data is that increasing the analytical sensitivity for HPV16 by AHPV GT might slightly increase the detection of CIN2+ among samples that were AHPV positive, while limiting the use of cobas HPV genotyping to only hrHPV positives would substantially reduce (by 33%) the detection of low-risk HPV16 infections by that test.

HPV18 and HPV45 detection by AHPV GT was more likely to test positive and detected more CIN2+ than HPV18 detection by cobas, presumably due to the inclusion of HPV45 with HPV18. However, we found there was comparable histological risk stratification for testing positive by HPV18 and HPV45 using AHPV GT and using cobas for HPV18 detection.

Two of the 6 CIN2+ cases in which only one test was negative were likely caused by untargeted low-risk HPV types, with the single positive test result due to cross-reactivity with an untargeted HPV type. For the remaining four CIN2+ cases, the hrHPV-negative result for one or the other assay was mostly likely due to a false-negative assay result, since the other methods for detecting hrHPV were positive for the hrHPV types. This could have been caused by differences in the hrHPV DNA viral load and E6/E7 RNA expression or by sampling error; however, there were insufficient numbers of discordant hrHPV results for CIN2+ (only 3 AHPV-positive [$AHPV^+$]/cobas-negative [$cobas^-$] and 3 $AHPV^-$/$cobas^+$) to explore these possibilities. The paired-negative test results could be either truly dual negative, i.e., the histology diagnosis was not correct, or could have CIN2+ caused by a borderline hrHPV type not targeted by these assays. For HPV test paired-negative results, it is well known that there are cases of CIN2/3 and even cancer caused by borderline-risk and even low-risk hrHPV genotypes (9–12) as well as morphological look-alikes of CIN2/3 that are probably metaplasia (12). Cases caused by borderline- or low-risk genotypes, although they are CIN2+, are rare; considering the prevalence of those types in invasive cervical cancer, neoplasia caused by these infections has low invasive potential. Of the cases that are probably metaplasia, the use of p16 immunohistochemistry would clarify their oncogenic potential (13). Alternatively, some of these lesions could be regressing due to host immune surveillance and clearance of the underlying viral infection (14). Of note in this regard, all of the AHPV-negative CIN2+ cases were also negative for hrHPV E6/E7 RNA by RT-PCR sequencing, suggesting the absence of active viral oncogene expression occurring even in the presence of viral genomic DNA. The HPV82-positive CIN3 case among the AHPV-positive/cobas-nega-

tive set may have been due to AHPV and HC2 detection of this untargeted, borderline hrHPV type, with which both tests have been reported to cross-react (15). A similar scenario can be envisioned for the CIN2 case among the AHPV-negative/cobas-positive set, in which HC2 was positive for a sample typed as low risk (HPV6 and HPV61) by LA yet which was positive by cobas for HPV18.

One limitation of this study was that specimens were collected from women at the colposcopy visit following referral for an ASC-US Pap result obtained from the baseline screening examination, which is not the intended use population. (hrHPV testing is indicated for screening women in conjunction with cytology and immediate triage of an ASC-US Pap result to decide who needs colposcopy.) However, the colposcopy visit was only about 1 month later on average; therefore, it seems likely that the results would be very similar to what would have been observed if performed on the baseline Pap specimen. To that point, there was no significant difference in the test positivity between AHPV performed on the baseline specimen and on the colposcopy specimen presented in this analysis (data not shown; manuscript in preparation). In addition, partial HPV genotyping for types 16, 18, and 45 is not recommended in the management of women with ASC-US Pap results, so future studies will need to compare the risk stratification achieved by partial HPV genotyping in a screening population to confirm the performance observed in this study.

In conclusion, hrHPV detection and risk stratification achieved by AHPV and AHPV GT and by cobas were comparable and very sensitive for CIN2+ and especially for CIN3+. Each test offers advantages. AHPV was more specific than cobas, while cobas provides simultaneous HPV16 and HPV18 detection rather than sequential testing with AHPV and AHPV GT to identify women with HPV16 and HPV18 (and HPV45). The tradeoffs in performance, benefits and harms, logistics, and costs should be considered in the choice of test and testing technology.

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P. E. Castle, J. Reid, D. Getman, and J. Dockter conceived the study, analyzed the results, and wrote the manuscript. B. Eaton organized the testing, analyzed the results, and reviewed the manuscript.

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