

Assessment of the Diagnostic Value of High-Risk HPV Molecular-based Methods for Triage of Iranian Women with Abnormal Cytological Findings of ASC-US and LSIL

Azam-Sadat Mousavi^{1,2,3*}, Setareh Akhavan¹, Fareideh Sabzi shahrbabaki⁴, Narges Izadi-mood⁵, Fariba Yarandi^{2,3,6}, Mehran Ghazimoghadam⁷, Mohammad Pouryasin⁸, Saina Nassiri⁴, Mamak Shariat⁹, Ali Pouryasin⁸

1. Department of Gynecology-Oncology, Vali-e-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran
2. National Association of Iranian Gynecologists and Obstetricians, Tehran, Iran
3. Iranian Society for Colposcopy and Cervical Pathology, Tehran, Iran
4. Department of Gynecology and Obstetrics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
5. Department of Pathology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
6. Department of Gynecology-Oncology, Yas Hospital, Tehran University of Medical Sciences, Tehran, Iran
7. Department of Pathology, Armin Pathobiology and Genetics Laboratory, Tehran, Iran
8. Department of Molecular Diagnosis, Armin Pathobiology and Genetics Laboratory, Tehran, Iran
9. Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Sciences, Tehran, Iran



Article Info

doi [10.30699/jogcr.7.3.151](https://doi.org/10.30699/jogcr.7.3.151)

Received: 2021/06/29;
Accepted: 2021/08/13;
Published Online: 12 Jan 2022;

Use your device to scan and read the article online



Corresponding Information:

Azam-Sadat Mousavi,
 Department of Gynecology-Oncology, Vali-e-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran
Email: Azamsadat_mousavi@yahoo.com

ABSTRACT

Background & Objective: Recent advances in molecular testing for human papillomavirus (HPV) has increased the accuracy of cervical screening programs. This study intended to estimate the diagnostic value of high-risk (HR) HPV DNA- and E6/E7 mRNA-based methods for triage of Iranian women with abnormal cytological results regarding the histopathological cut-off.

Materials & Methods: In this cross-sectional study, 360 non-pregnant women (≥ 21 years) who had faced abnormal cytological findings (ASC-US and LSIL) were enrolled and referred for further diagnostic tests. The INNO-LiPA® HPV Genotyping Extra-II and Aptima HPV assay kits were used in DNA- and E6/E7 mRNA-based methods for detection of HR-HPV. Regarding the CIN-2+ histopathological cut-off, the diagnostic value of each molecular-based assay was calculated.

Results: Among the study participants, 260 cases had ASC-US, and 100 had LSIL. The overall positivity rate for DNA- and mRNA-based methods was 74.4% (268/360) and 64.2% (231/360), respectively. Fifty-nine (16.4%) individuals showed CIN-2+. The DNA-based test showed higher sensitivity (100%) than the mRNA-based method (93.2%), while the mRNA-based method revealed greater clinical specificity (41.5%) compared to the DNA-based test (30.6%).

Conclusion: Our results revealed appropriate clinical sensitivity of the molecular-based methods for triage of Iranian women with abnormal cytological results; however, the mRNA-based method showed greater specificity for detection of CIN-2+.

Keywords: ASC-US, Cervical Intraepithelial Neoplasia (CIN), Human Papillomavirus (HPV), LSIL, Molecular-based methods



Copyright © 2022, This is an original open-access article distributed under the terms of the Creative Commons Attribution-noncommercial 4.0 International License which permits copy and redistribution of the material just in noncommercial usages with proper citation.

Introduction

Cervical cancer (CC) is the fourth most common type of cancer among women. In 2018, near 569,000 women were diagnosed with this cancer, and 311,000 deaths from CC were recorded (1). Infection with human papillomavirus (HPV), especially the high-risk (HR) genotypes, is the predominant cause of CC (2). Based on the studies and according to the clinical

pathogenicity of HPV genotypes, types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 could be considered as the HR genotypes, and persistent infection with these genotypes is highly associated with CC progression (3-5). There are various screening approaches available for the early detection and prevention of CC. The cervical cytology test

considerably decreased CC and mortality rates by 79% and 70%, respectively. Due to the higher rate of false-negative results of this test, screening tests with higher clinical sensitivity have been suggested. To confirm the abnormal findings during the screening process, colposcopy, and if needed, histopathological examination of the cervix should be performed (6-9). Recent advances in molecular testing of HPV have increased the accuracy of cervical screening programs (10, 11); therefore, doing HR-HPV tests as well as cytological testing of the cervix at the same time (co-test) have been commonly used as acceptable approaches for CC screening and evaluating patients who face abnormal cytological results (12).

Although the combination of DNA-based methods for detecting HR-HPV genotypes with the cytological testing of the cervix has increased the sensitivity of CC screening (13-15), higher clinical sensitivity may reduce the clinical specificity of DNA-based methods for the determination of cervical intraepithelial neoplasia (CIN). On the other hand, almost all of the HPV infections could be resolved spontaneously; hence the positive result for the HR-HPV DNA test cannot be considered as CIN (16, 17). Since the development of CC depends on the activity of E6/E7 oncoproteins, the mRNA assessment of these proteins could exhibit improved specificity compared to the HR-HPV DNA test for predicting moderate to severe cervical dysplasia (18-21).

Considering that a few data are available in surveys about the evaluation of diagnostic value of HPV molecular-based tests in our region and that patients with transient HR-HPV infections are at risk of overtreatment, we evaluated the HR-HPV DNA- and E6/E7 mRNA-based assays as well as doing histopathological evaluation of cervix in women who had abnormal cytological findings as atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL) to estimate the diagnostic value of these methods for triage of Iranian women in our region.

Materials and Methods

Study Participants and Design

First, 7907 Iranian women (≥ 21 years) who had referred to Vali-e-Asr Hospital from Apr 2017 to March 2021 enrolled in this cross-sectional study. Out of the enrolled women, 360 non-pregnant women who had abnormal cytological results (ASC-US and LSIL) were selected based on the inclusion criteria, and an informed consent was obtained from them. They accepted to refer for further diagnostic tests. While patients with a history of HPV vaccination, pre-cancerous change of the cervix, cervical cancer, abnormal Pap test in the last 12 months, hysterectomy, immunological abnormalities, or disorders were excluded. The Ethics Committee of Imam Khomeini Hospital Complex approved this research protocol (IR.TUMS.IKHC.REC.1399.140).

Sample Collection, Preparation, and Routine Cervical Screening at the Baseline

The cervical specimen was collected and subjected to cytological testing using the ThinPrep® (TP) PreserCyt solution (Hologic, Inc. USA). The TP 2000 system (Hologic, Inc. USA) was used to prepare the Pap test slides. Slide preparation and staining procedure were performed according to the TP staining protocols. Two different cytopathologists evaluated the slides based on the Bethesda 2014 system.

Colposcopy, Histopathological and Molecular HPV Assessment During the Second Visit

For evaluating the molecular-based HPV tests, gynecological specimens were collected in TP vials containing PreserCyt solution (Hologic, Inc. USA). To do the HR-HPV DNA-based test, an appropriate amount of the specimens were stored at -24°C . According to the Aptima HPV assay kit protocol (Hologic, Inc. USA), 1 mL of the specimens was transferred into the Aptima specimen transfer tube and stored at $2-8^{\circ}\text{C}$. The gynecologic oncologists of Vali-e-Asr Hospital did the colposcopy and cervical biopsy. Briefly, during this process, the cervical tissues of the patients without any signs of abnormalities were randomly biopsied in four-quadrant positions of the transformation zone. In contrast, multiple biopsies were taken from abnormal areas of patients with any signs of abnormal colposcopy features. After formalin fixation, biopsies were paraffin embedded, slides were prepared, and hematoxylin and eosin staining was done. Then two different gynecologic pathologists evaluated the specimens according to the related classification system (22). The CIN-2 or higher pathological grades were considered positive, and other results were considered negative for histopathological findings. The HR-HPV molecular-based methods, including the HR-HPV DNA- and E6/E7 mRNA-based tests, were done as described by Mousavi *et al.* (23).

Statistical Analysis

The mean age \pm standard deviation (SD) was calculated for the participants. The positivity rate of the molecular-based methods, and cytological and histopathological results were calculated by frequency. The agreement between the molecular-based methods was calculated using the Kappa coefficient. Regarding Altman's classification method, k represents the agreement. Very good agreement is observed when the k is 0.8 or higher (24). Regarding the pathological cut-off, the diagnostic value of each molecular-based method was calculated. For this purpose, negative predictive value (NPV), positive predictive value (PPV), clinical specificity (true negative rate), clinical sensitivity (true positive rate), and 95% confidence interval (95% CI) were calculated for each molecular-based assay. Statistical analyses were performed using the STATA statistical package for Windows (Ver. 13, Released 2013, StataCorp L.P., College Station, Texas, USA) and SPSS 21 (IBM Corp, Armonk, New York, USA).

Results

The mean age of participants was 34.76±7.00 years. The cytological assessment showed that 260 individuals (72.2%) had ASC-US, and 100 (28.8%) had LSIL. The total positivity rate of the DNA-based test using the INNO-LiPA® HPV Genotyping Extra-II kit was 74.4% (268/360). This method showed 183 cases of HR-HPV-infected individuals (70.4%) had ASC-US; however, this infection rate was observed for 85 individuals (85.0%) with LSIL. The overall positivity rate of the mRNA-based method using the Aptima HPV assay was 64.2% (231/360). Among the individuals with ASC-US, 154 cases (59.2%) showed positive mRNA-based results; however, among the patients with LSIL, 77 cases (77.0%) showed a positive result for mRNA-based assay. [Table 1](#) shows the concordance between the molecular-based tests regarding the kappa statistic.

The histopathological assessment showed 198 participants (55.0%) had normal results, 103 (28.6%) had CIN-1, and 59 (16.4%) had CIN-2 or high grade CIN-2+. Among the individuals with ASC-US, 156 (60.0%), 59 (22.7%), and 45 (17.3%) individuals revealed normal results, CIN-1, and CIN-2+, respectively. However, histopathological findings for the LSIL group showed that 42 (42.0%), 44 (44.0%), and 14 (14.0%) individuals had normal results, CIN-1, and CIN-2+, respectively. The diagnostic value of each method was assessed regarding CIN-2+ histopathological cut-off. The ratio of positivity for each molecular-based method regarding the histopathological cut-off sorted by cytological grades is shown in [Table 2](#).

[Table 3](#) demonstrates the clinical sensitivity, specificity, and positive and negative predictive values of each HPV molecular-based assay regarding the histopathological cut-off.

Table 1. Agreement percentage between the molecular-based methods

Groups	Positive cases (%)		DNA-, mRNA-	DNA+, mRNA-	DNA-, mRNA+	DNA+, mRNA+	% Agreement	Kappa	P-value
	DNA+	mRNA+							
ASC-US n=260	183 (70.4)	154 (59.2)	76	30	1	153	88.09	0.74	<0.001
LSIL n=100	85 (85.0)	77 (77.0)	13	10	2	75	88.00	0.61	<0.001
All n=360	268 (74.4)	231 (64.2)	89	40	3	228	88.06	0.72	<0.001

DNA-, Negative result for DNA-based method; mRNA-, Negative result for mRNA-based method; DNA+, Positive result for DNA-based method; mRNA+, Positive result for mRNA-based method.

Table 2. Positivity rates of the molecular-based methods of HR-HPV regarding the histopathological cut-off

Group	Histopathological Result	Positive cases (%)	
		DNA+	mRNA+
ASC-US (n=260)	Negative n=215	138 (64.2)	113 (52.6)
	Positive n=45	45 (100.0)	41 (91.1)
	All n=260	183 (70.4)	154 (59.2)
	Negative n=86	71 (82.6)	63 (73.3)
LSIL (100)	Positive n=14	14 (100.0)	14 (100.0)
	All n=100	85 (85.0)	77 (77.0)
	Negative n=301	209 (69.4)	176 (58.5)
	Positive n=59	59 (100.0)	55 (93.2)
Total (360)	All n=360	268 (74.4)	231 (64.2)

Negative histopathological result, <CIN-2; Positive histopathological result, CIN-2+; DNA+, Positivity rate of DNA-based method; mRNA+, Positivity rate of mRNA-based method.

Table 3. The diagnostic value of each HPV molecular-based assay based on the CIN-2+ cut-off

Diagnostic value	ASC-US (n=260)		LSIL (100)		Total (360)	
	DNA	mRNA	DNA	mRNA	DNA	mRNA
Clinical Sensitivity (95% CI)	100.0	91.1 (82.8-99.4)	100.0	100.0	100.0	93.2 (86.8-99.6)
Clinical specificity (95% CI)	35.8 (29.4-42.2)	47.4 (40.8-54.1)	17.4 (9.4-25.5)	26.7 (17.4-36.1)	30.6 (25.4-35.8)	41.5 (36.0-47.1)
Positive predictive value (95% CI)	24.6 (18.4-30.8)	26.6 (19.6-33.6)	16.5 (8.6-24.4)	18.2 (9.6-26.8)	22.0 (17.1-27.0)	23.8 (18.3-29.3)
Negative predictive value (95% CI)	100.0	96.2 (92.6-99.9)	100.0	100.0	100.0	96.9 (94.0-99.9)

DNA, DNA-based method; mRNA, mRNA based method

Discussion

The study aimed to determine the diagnostic value of DNA- and E6/E7 mRNA-based methods in detection of HR-HPV for triage of women who had faced abnormal cytological results (ASC-US and LSIL). Among the study participants, the overall positivity rate of DNA- and mRNA-based methods was 74.4% and 64.2%, respectively. As expected, and illustrated in Tables 1 and 2, the positivity rate of both methods increased in more severe cytological (LSIL compared to ASC-US) and histopathological (positive compared to the negative histopathological cut-off) grades. The majority of previous studies have found a similar positivity pattern. For example, a recent study in our region that used the Cobas HPV DNA test showed positivity rates of 54.2% and 66.6% for HR-HPV DNA-based test for ASC-US and LSIL groups, respectively (25). In a study that assessed the diagnostic value and performance of HR-HPV DNA- and E6/E7 mRNA-based methods for managing the women referred for colposcopy, the positivity rate of DNA- and mRNA-based tests using the Cobas HPV DNA and Aptima HPV assays were 41.7% and 25% for the patients with normal histopathological results, while these positivity rates were 82.9% and 84.3% for the patients with CIN-2; and 100.0% and 98.1% for the patients with CIN-3+ (26).

Due to the different positivity rates obtained for the two methods, not a very good agreement was observed ($0.6 \leq k < 0.8$). Other similar results were recently reported between the two mentioned methods among Iranian women with NILM cytological results (23). These findings were observed as a result of the different invention basis of the two mentioned methods. Briefly, in this study, the DNA-based test was done using the INNO-LiPA® HPV Genotyping Extra-II kit, which uses the PCR technique for amplifying 65 bps of the L1 region of HPV, and the higher power for detection of the viral particle is expected, while the Aptima HPV assay was used to detect the E6/E7 mRNA of HPV, which uses the signal to the cut-off (S/CO) calculation to detect the CINs, and higher clinical specificity and lower sensitivity are expected. The higher positivity rate of the DNA-based method

compared to the mRNA-based assay was also observed among the Iranian women with NILM cytological results (23). These findings confirmed this idea that the HR-HPV-mRNA detection might be less sensitive and more specific for detection of the CINs compared to the highly sensitive DNA-based PCR assays.

As shown in Table 3, the overall clinical sensitivity and NPV of the DNA-based method were higher than those of the mRNA-based assay, while the mRNA-based assay showed better PPV and clinical specificity for the detection of CIN-2+. So far, many studies have assessed the diagnostic value and clinical performance of several kinds of HR-HPV DNA- and mRNA-based assays for the detection of CIN-2+. Szarewski *et al.* found that the DNA-based method (Cobas HPV test) compared to the mRNA-based method (Aptima HPV assay) showed a higher sensitivity (94.9% versus 92.3%) and a lower specificity (25.1% versus 29.1%) in detection of CIN-2+ (27). This pattern was also observed for our data, as we found 100% clinical sensitivity for the DNA-based test and 93.2% for the mRNA-based assay. Although both studies showed a higher clinical sensitivity for the DNA-based test compared to the mRNA-based assay, we found a higher clinical sensitivity for the DNA-based method in contrast to the Cobas HPV test (27). This difference is explained by different goals defined for each HR-HPV DNA-based method. As mentioned above, we used one of the highly sensitive commercially approved PCR-based methods to detect HR-HPV genotypes, while the Cobas HPV test employs the clinical cut-off value for the detection of CIN-2+ (28).

In this study, among the patients with ASC-US, a higher clinical sensitivity was observed for the DNA-based test compared to the mRNA-based method (100.0% vs. 91.1%). Moreover, the mRNA-based method showed higher clinical specificity than the DNA-based method (47.4% vs. 35.8%). Although the low number of CIN-2+ cases among the patients with LSIL made it difficult to determine the actual clinical performance of each method, the mRNA-based method showed the same clinical sensitivity and higher clinical

specificity in comparison with the DNA-based method (Table 3). Castle *et al.* found equal clinical sensitivity for DNA- and mRNA-based methods in determination of CIN-2+ among women referred for colposcopy procedure following the ASC-US cytological results (89.4% vs. 91.4%) (29). However, the mentioned studies showed higher specificity for the mRNA-based method (42.0% vs. 63.1%) compared to the DNA-based method (31.2% vs. 59.3%) (29). This clinical performance pattern was also observed among several other studies, which compared the diagnostic value of different types of molecular methods for the detection of CIN-2+ (26, 27, 30, 31) and highly suggested the E6/E7 mRNA-based method for triage of women with abnormal cytological findings.

Although our results revealed valuable data for triage of Iranian women who had faced abnormal cytological results, follow-up of the study participants should be conducted to evaluate the long-term clinical performance of each method. At the moment, our data showed good clinical sensitivity and higher clinical specificity for the mRNA-based assay rather than the DNA-based test in detecting CIN-2+. Furthermore, low number of participants, especially in the LSIL group, may affect our assessment of the diagnostic value of each method; hence further studies with higher number of participants and enrollment of other cytological groups from Iranian women are highly recommended. Moreover, according to the availability of commercial

molecular HPV kits in our region, evaluation of other DNA-based methods, especially those that use the clinical cut-off value and are validated for detecting the CINs, is highly suggested.

Conclusion

The HR-HPV DNA-based detection method using the INNO-LiPA® HPV Genotyping Extra-II kit and the HR-HPV E6/E7 mRNA-based detection method using the Aptima HPV assay kit revealed appropriate clinical sensitivity for detection of CIN-2+ among the Iranian women with ASC-US and LSIL cytological results. The HR-HPV mRNA-based assay displayed a higher clinical specificity for detecting CIN-2+ compared to the HR-HPV DNA-based method. Therefore, using molecular-based methods for triage of Iranian women with abnormal cytological results is highly recommended.

Acknowledgments

We would like to thank all the gynecologists, gynecologist-oncologists, cytopathologists, gynecological-pathologists, and laboratory technicians for helping us with this project.

Conflict of Interest

The authors declared no conflicts of interest.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8):1941-53. [DOI:10.1002/ijc.31937] [PMID]
2. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189(1):12-9. [DOI:10.1002/(SICI)1096-9896(199909)189:13.0.CO;2-F]
3. Humans IWGotEoCRt. Biological agents. Volume 100 B. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum. 2012;100(Pt B):1-441.
4. Bzhalava D, Guan P, Franceschi S, Dillner J, Clifford G. A systematic review of the prevalence of mucosal and cutaneous human papillomavirus types. *Virology*. 2013;445(1-2):224-31. [DOI:10.1016/j.virol.2013.07.015] [PMID]
5. Moscicki AB, Schiffman M, Burchell A, Albero G, Giuliano AR, Goodman MT, et al. Updating the natural history of human papillomavirus and anogenital cancers. *Vaccine*. 2012;30 Suppl 5:F24-33. [DOI:10.1016/j.vaccine.2012.05.089] [PMID] [PMCID]
6. Correa Mda S, Silveira DS, Siqueira FV, Facchini LA, Piccini RX, Thume E, et al. [Pap test coverage and adequacy in the South and Northeast of Brazil]. *Cad Saude Publica*. 2012;28(12):2257-66. [DOI:10.1590/S0102-311X2012001400005] [PMID]
7. Chen YC, Liu HY, Li CY, Lee NY, Ko WC, Chou CY, et al. Low Papanicolaou smear screening rate of women with HIV infection: a nationwide population-based study in Taiwan, 2000-2010. *J Womens Health (Larchmt)*. 2013;22(12):1016-22. [DOI:10.1089/jwh.2012.4127] [PMID] [PMCID]
8. Bobdey S, Sathwara J, Jain A, Balasubramaniam G. Burden of cervical cancer and role of screening in India. *Indian J Med Paediatr Oncol*. 2016;37(4):278-85. [PMID] [PMCID] [DOI:10.4103/0971-5851.195751]
9. Geldenhuys L, Murray ML. Sensitivity and specificity of the Pap smear for glandular lesions of the cervix and endometrium. *Acta Cytol*.

- 2007;51(1):47-50. [[DOI:10.1159/000325682](https://doi.org/10.1159/000325682)] [[PMID](#)]
10. Boulet GA, Horvath CA, Berghmans S, Bogers J. Human papillomavirus in cervical cancer screening: important role as biomarker. *Cancer Epidemiol Biomarkers Prev.* 2008;17(4):810-7. [[DOI:10.1158/1055-9965.EPI-07-2865](https://doi.org/10.1158/1055-9965.EPI-07-2865)] [[PMID](#)]
 11. Stoler MH, Wright TC, Jr., Cuzick J, Dockter J, Reid JL, Getman D, et al. APTIMA HPV assay performance in women with atypical squamous cells of undetermined significance cytology results. *Am J Obstet Gynecol.* 2013;208(2):144 e1-8. [[DOI:10.1016/j.ajog.2012.12.003](https://doi.org/10.1016/j.ajog.2012.12.003)] [[PMID](#)]
 12. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis.* 2013;17(5 Suppl 1):S1-S27. [[PMID](#)] [[DOI:10.1097/LGT.0b013e318287d329](https://doi.org/10.1097/LGT.0b013e318287d329)]
 13. Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer.* 2006;119(5):1095-101. [[DOI:10.1002/ijc.21955](https://doi.org/10.1002/ijc.21955)] [[PMID](#)]
 14. Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med.* 2007;357(16):1579-88. [[DOI:10.1056/NEJMoa071430](https://doi.org/10.1056/NEJMoa071430)] [[PMID](#)]
 15. Baseman JG, Kulasingam SL, Harris TG, Hughes JP, Kiviat NB, Mao C, et al. Evaluation of primary cervical cancer screening with an oncogenic human papillomavirus DNA test and cervical cytologic findings among women who attended family planning clinics in the United States. *Am J Obstet Gynecol.* 2008;199(1):26 e1-8. [[DOI:10.1016/j.ajog.2007.11.051](https://doi.org/10.1016/j.ajog.2007.11.051)] [[PMID](#)]
 16. Moscicki AB, Ma Y, Jonte J, Miller-Benningfield S, Hanson E, Jay J, et al. The role of sexual behavior and human papillomavirus persistence in predicting repeated infections with new human papillomavirus types. *Cancer Epidemiol Biomarkers Prev.* 2010;19(8):2055-65. [[DOI:10.1158/1055-9965.EPI-10-0394](https://doi.org/10.1158/1055-9965.EPI-10-0394)] [[PMID](#)] [[PMCID](#)]
 17. Goodman MT, Shvetsov YB, McDuffie K, Wilkens LR, Zhu X, Thompson PJ, et al. Prevalence, acquisition, and clearance of cervical human papillomavirus infection among women with normal cytology: Hawaii Human Papillomavirus Cohort Study. *Cancer Res.* 2008;68(21):8813-24. [[DOI:10.1158/0008-5472.CAN-08-1380](https://doi.org/10.1158/0008-5472.CAN-08-1380)] [[PMID](#)] [[PMCID](#)]
 18. Cuschieri K, Wentzensen N. Human papillomavirus mRNA and p16 detection as biomarkers for the improved diagnosis of cervical neoplasia. *Cancer Epidemiol Biomarkers Prev.* 2008;17(10):2536-45. [[DOI:10.1158/1055-9965.EPI-08-0306](https://doi.org/10.1158/1055-9965.EPI-08-0306)] [[PMID](#)] [[PMCID](#)]
 19. Lie AK, Risberg B, Borge B, Sandstad B, Delabie J, Rimala R, et al. DNA- versus RNA-based methods for human papillomavirus detection in cervical neoplasia. *Gynecol Oncol.* 2005;97(3):908-15. [[DOI:10.1016/j.ygyno.2005.02.026](https://doi.org/10.1016/j.ygyno.2005.02.026)] [[PMID](#)]
 20. Sorbye SW, Fismen S, Gutteberg TJ, Mortensen ES, Skjeldestad FE. HPV mRNA is more specific than HPV DNA in triage of women with minor cervical lesions. *PLoS One.* 2014;9(11):e112934. [[DOI:10.1371/journal.pone.0112934](https://doi.org/10.1371/journal.pone.0112934)] [[PMID](#)] [[PMCID](#)]
 21. Austin RM. (2018) Technology matters: The clinical utility of HPV mRNA testing compared to DNA testing. Promotional supplement to Contemporary OB/GYN.
 22. Kurman RJ CM, Herrington CS. World Health Organisation Classification of Tumours of the Female Reproductive Organs. 4th Revised ed. International Agency for Research on Cancer, 2014.
 23. Mousavi AS, Pouryasini A, Yarandi F, Pirzadeh L, Alipour A, Khodadad S, et al. Assessment of Cervical Cancer Molecular-Based Screening Tools; HPV-DNA Detection versus E6/E7 mRNA Testing; First Report of a Prospective Cohort Study among Iranian Women. *Iran J Public Health.* 2020;49(9):1734-42. [[DOI:10.18502/ijph.v49i9.4093](https://doi.org/10.18502/ijph.v49i9.4093)]
 24. Szklo M NF, Reilly T, Parker K (2014). *Epidemiology : beyond the basics.* 4th Edition. ISBN-10: 128411659X.
 25. Jamdar F, Farzaneh F, Navidpour F, Younesi S, Balvayeh P, Hosseini M, et al. Prevalence of human papillomavirus infection among Iranian women using COBAS HPV DNA testing. *Infect Agent Cancer.* 2018;13:6. [[DOI:10.1186/s13027-018-0178-5](https://doi.org/10.1186/s13027-018-0178-5)] [[PMID](#)] [[PMCID](#)]
 26. Tewari P, White C, Kelly L, Pilkington L, Keegan H, D'Arcy T, et al. Clinical performance of the Cobas 4800 HPV test and the Aptima HPV assay in the management of women referred to colposcopy with minor cytological abnormalities. *Diagn Cytopathol.* 2018;46(12):987-92. [[DOI:10.1002/dc.24066](https://doi.org/10.1002/dc.24066)] [[PMID](#)]
 27. Szarewski A, Mesher D, Cadman L, Austin J, Ashdown-Barr L, Ho L, et al. Comparison of seven tests for high-grade cervical intraepithelial neoplasia in women with abnormal smears: the Predictors 2 study. *J Clin Microbiol.* 2012;50

- (6):1867-73. [[DOI:10.1128/JCM.00181-12](https://doi.org/10.1128/JCM.00181-12)] [[PMID](#)] [[PMCID](#)]
28. cobas® 4800 HPV Test [package insert]. Branchburg NRMS, Inc; 2018.
29. Castle PE, Reid J, Dockter J, Getman D. The reliability of high-risk human papillomavirus detection by Aptima HPV assay in women with ASC-US cytology. *J Clin Virol.* 2015;69:52-5. [[DOI:10.1016/j.jcv.2015.05.006](https://doi.org/10.1016/j.jcv.2015.05.006)] [[PMID](#)]
30. Moss SM, Bailey A, Cubie H, Denton K, Sargent A, Muir P, et al. Comparison of the performance of HPV tests in women with abnormal cytology: results of a study within the NHS cervical screening programme. *Cytopathology.* 2015;26(6):373-80. [[DOI:10.1111/cyt.12210](https://doi.org/10.1111/cyt.12210)] [[PMID](#)]
31. Ovestad IT, Vennestrom U, Andersen L, Gudlaugsson E, Munk AC, Malpica A, et al. Comparison of different commercial methods for HPV detection in follow-up cytology after ASCUS/LSIL, prediction of CIN2-3 in follow up biopsies and spontaneous regression of CIN2-3. *Gynecol Oncol.* 2011;123(2):278-83. [[DOI:10.1016/j.ygyno.2011.07.024](https://doi.org/10.1016/j.ygyno.2011.07.024)] [[PMID](#)]

How to Cite This Article:

Mousavi AS, Akhavan S, Sabzi shahrbabaki F, Izadi-mood N, Yarandi F, Ghazimoghadam M, et al. Assessment of the Diagnostic Value of High-Risk HPV Molecular-based Methods for Triage of Iranian Women with Abnormal Cytological Findings of ASC-US and LSIL. *J Obstet Gynecol Cancer Res.* 2022; 7 (3) :151-157

Download citation:

[BibTeX](#) | [RIS](#) | [EndNote](#) | [Medlars](#) | [ProCite](#) | [Reference Manager](#) | [RefWorks](#)