COMBO TEST PLUS: SAFETY FOR THE PATIENT, PEACE OF MIND FOR THE GYNECOLOGIST

LAMM

LABORATORIO ANALISI MEDICHE MARTINI
IMPACTLABgroup

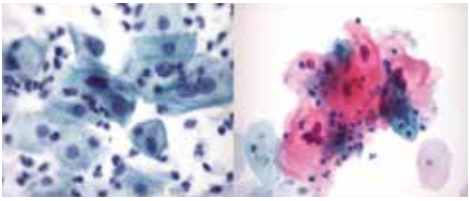
BEYOND THE PAP-TEST IN THE PREVENTION OF THE CERVICAL CARCINOMA: THE COMBO TEST-PLUS

Some genotypes of human paillomavirus (HPV) may cause the cervical carcinoma. Once present in the vaginal cavity, HPV can infect the cervical epithelium, entering in the cell and integrating its DNA into the human one. Even if it is often self-limited, HPV must not be underevaluated: indeed HPV infection cannot be strictly defines as a sexual trasmitted disease, because this virus can reach the vaginal cavity in a number of other ways (sanitary napkin, vaginal lavage, suppositories etc).

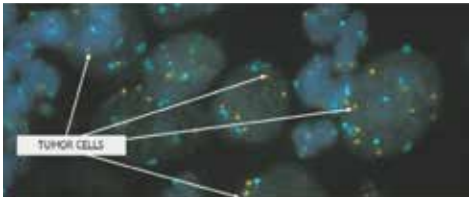
By means of the Combo Test-Plus, together with the so called liquid pap-test (which represents the gold standard for the examination of the cervical cells), a molecular test (**Aptima® HPV assay, Hologic®, USA**) for the detection of the RNA of the 14 high risk genotypes of papillomavirus (HPV) is carried out. The presence of HPV RNA proves not only the presence of the HPV but above all the integration of viral DNA into the human one and, therefore, the production of the viral proteins that can start the progression to cancer. This double approach increases the sentitivity of the screening to the maximum level, therefore the likelihood of false negative is minimal.

In case the screening reveals a L-SIL (low squamous intraepithelial lesions) with or without the presence of HPV RNA, the Combo Test-Plus includes the FISH of the cervical cells as a reflex test, which is carried out for free and without to repeat the cells collection. The FISH (Fluorescence In Situ Hybridization), a well established pathology technique, allows to enumerate, directly into the cells, the chromosomes whose number typically increases when the cell becomes malignant. Therefore, by means of FISH it is possible to identify certain tumor cells, despite their morphological appearance is only atypical.

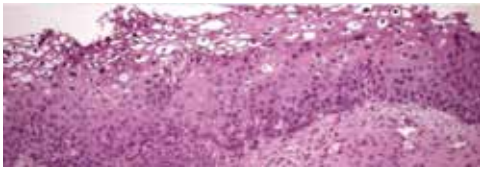
The Combo Test-Plus allows to anticipate the diagnosis, reducing invasivity, costs and response time and therefore represents the most advanced screening method for cervical cancer.



LSIL with koilocytes



The FISH performed on the same cervical cells shows their tumoral nature (polisomy)



Biopsy revealed CIN 1-2 with koilocytes

GENERAL INFORMATION ABOUT TESTS PERFORMED

In **Laboratorio Analisi Mediche Martini**, the pap-test is performed in a liquid phase, starting by cervical cells collected by brushing and maintained in Thin PrepÒ container at room temperature; cells are filtered by mean of Thin Prep 5000 sample transfer system and the thin layer slide is then stained and evaluated microscopically by a specialized cytologist. All the abnormal cases are reviewed by a pathologist which, anyway, review the 10% of all the cases, as per recommended quality policy.

In **Laboratorio Analisi Mediche Martini, Aptima® HPV assay** is used.

The **Aptima® HPV assay** is an *in vitro* nucleic acid amplification test for the qualitative detection of E6/E7 viral messenger RNA (mRNA) from 14 high-risk types of human papillomavirus (HPV) in cervical specimens. The high-risk HPV types detected by the assay include: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. The Aptima HPV assay does not discriminate between the 14 high-risk types. Cervical specimens in ThinPrep Pap Test vials containing PreservCyt Solution and collected with broom-type or cytobrush/spatula collection devices* may be tested with the Aptima HPV assay. The assay is used with the Panther System.

The use of the test is indicated:

1. To screen women 21 years and older with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results to determine the need for referral to colposcopy. The results of this test are not intended to prevent women from proceeding to colposcopy.
2. In women 30 years and older, the Aptima HPV assay can be used with cervical cytology to adjunctively screen to assess the presence or absence of high-risk HPV types. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

* Broom-type device (e.g., Wallach Pipette) or endocervical brush/spatula.

Bibliography

1. **Doorbar, J.** Clin Sci (Lond). 2006:110(5):525-41.
2. **Monsonego J. et Al.** Int J Cancer. 2004: 108(3):329-33.
3. **Walboomers, J. M. et Al.** J Pathol. 1999:189:12-19.
4. **Lambert P.F. et Al.** Proc Natl Acad Sci U S A. 1993: 90(12):5583-7.
5. **Kjaer S.K.et Al.** BMJ. 2002: 325(7364): 572-579.
6. **Burd, E.M.** Clin Microbiol Rev. 2003:16(1):1-17.
7. **Li N. et Al.** Int J Cancer, 2010 n/a. doi: 10.1002/ijc.25396.
8. **Cuschieri, K.S.et Al.** J. Med. Virol.2004: 73(1): 65-70.
9. **Baseman, J.G. et Al.** J Clin Virol. 2005:32 Suppl 1:S16-24.
10. **Czegledy J. et Al.** Int J Cancer. 1995:64(3):211-5.
11. **Kacian, D.L. et Al.** U. S. Patent 5,399,491.
12. **Arnold, L.J. et Al.** Clin Chem. 1989:35: 1588-1594.
13. **Nelson, N.C. et Al.** Biochem. 1996:35:8429-8438.
14. **Wright T.C. et Al.** Am J Obstet Gynecol 2007:197 (4); 346-355.
15. **Datta, S. D. et Al.** Annals Int Med. 2008:148:493.
16. **Clifford, G.M. et Al.** The Lancet. 2005:366, 991.
17. **Stoler, M.H. et Al.** Am J Obstet & Gynecol. 2013:208(2):144-145.
18. **Pretorius R.G. et Al.** Am J Obstet Gynecol. 2004:191:430-434.
19. **Pretorius R.G. et Al.** J Low Genit Tract Dis. 2006:10(1):5-9.
20. **Kondratovich, M.V. et Al.** ASA Section on Statistics in Epidemiology. 2005:901:2547-2551.
21. **Hopman A.H.N. et Al.** *J Pathol*. 2006;210:412-419.
22. **Sokolova I et al.** *J Mol Diagn*. 2007;9:604-611.
23. **Heselmeyer-Haddad K. et Al.** *Am J Pathol*. 2005;166:1229-1238.
24. **Alameda F et Al.** *Hum Pathol*. 2009;40:1474-1478.
25. **Yin et Al.** World Journal of Surgical Oncology 2012, 10:168

WARNING

This assay is not intended for use as a screening device for women under age 30 with normal cervical cytology.

The Aptima HPV assay is not intended to substitute for regular cervical cytology screening.

Detection of HPV using the Aptima HPV assay does not differentiate HPV types and cannot evaluate persistence of any one type.

The use of this assay has not been evaluated for the management of HPV vaccinated women, women with prior ablative or excisional therapy, hysterectomy, who are pregnant, or who have other risk factors (e.g., HIV+, immunocompromised, history of sexually transmitted infection).

The Aptima HPV assay is designed to enhance existing methods for the detection of cervical disease and should be used in conjunction with clinical information derived from other diagnostic and screening tests, physical examinations, and full medical history in accordance with appropriate patient management procedures.

Test only the indicated specimen type. The Aptima HPV assay has only been validated for use with cervical specimens collected in PreservCyt Solution using a broom-type or cytobrush/spatula collection device.

Collect cervical specimens in ThinPrep Pap Test vials containing PreservCyt Solution with broom-type or cytobrush/spatula collection devices according to the manufacturer's instructions. Aliquots subsequently removed from the ThinPrep Pap Test vial for testing with the Aptima HPV assay should be processed using only the Aptima Specimen Transfer Kit.

In **Laboratorio Analisi Mediche Martini**, the **FISH** (Fluorescence In Situ Hibrydization) **of cervical cells**, is performed targeting the 3q26 and the CEP7, by mean of a LDT (Laboratory Developed Test) whose accuracy is warranted by a double in parallel evaluation of the samples (firstly by a specialized Science Doctor and secondly by Medicine Doctor specialized in Human Genetics): the use of Leica automated fluorescent microscopes, which allow the acquisition of a huge number of images, warrants the maximum of sensitivity.

GENERAL INFORMATION ABOUT LABORATORIO ANALISI MEDICHE MARTINI (LAMM)

Laboratorio Analisi Mediche Martini (LAMM) is a clinical laboratory located in Milan Italy); LAMM, part of Impact Lab Group, is authorised, according with the Italian Laws, as a general clinical laboratory with specialized sections of pathology, microbiology and virology. LAMM is accredited by the Italian Health System.

LAMM has two productive sites: the general laboratory is located in Milan, via Oltrocchi 11, while the pathology section occupies 320 sqm in the Filarete Foundation's buiding, a science park belonging to the University of Milan, in Milan, viale Ortles 22/4.

LAMM activities are covered by a specific professional insurance which includes also the genetic tests run for foreign customers.

LAMM tests are distributed in Lebanon by Biofinpharma Middle East (MOH authorization number 578/2 19.03.2007)

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