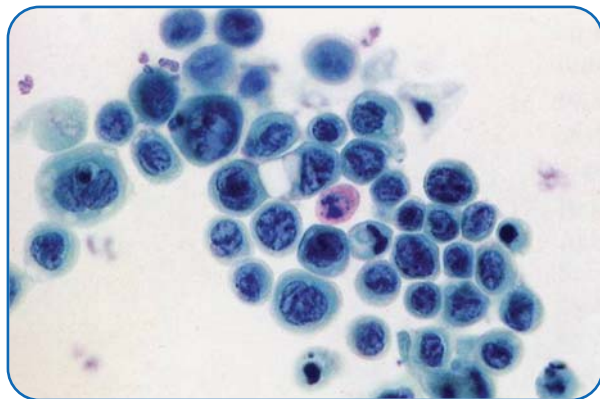
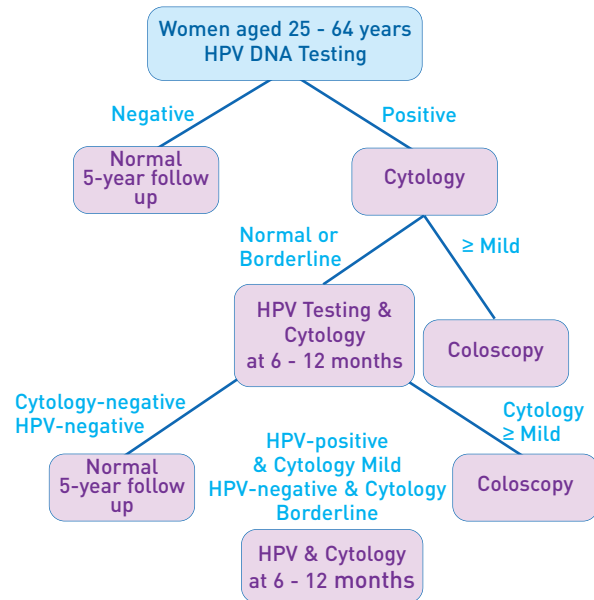


## HPV DNA testing in clinical practice

- HPV DNA testing for use in primary screening as an adjunct to cytology testing has been approved by the Food and Drug Administration and recommended for women of 30 years of age and over. Testing for HPV DNA is recommended in the follow-up of women treated for CIN2+ and in the triage of women with equivocal cytology results [atypical squamous cells of undetermined significance, also called ASCUS].

- See below; a proposed screening algorithm. From Cuzick et al., 2008. Vaccine.26 S10:K29-41.



## References

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- Meijer, C.J, Berkhof, J., Castle, P.E., Hesselink, A.T., Franco, E.L., Ronco, G., Arbyn, M., Bosch, F.X., Cuzick, J., Dillner, J., Heideman, D.A., Snijders, P.J. 2009. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *Int J Cancer*. 124, 516-20.

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# Focus on...



## Human papillomavirus and cervical cancer screening

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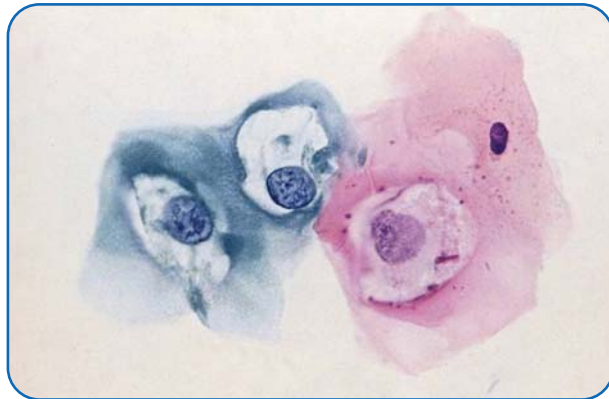
## Cervical cancer

- Cervical cancer is the second most common cancer among women worldwide with an estimated 493,000 new cases per year and approximately 270 000 deaths occurring annually.

- Epidemiological and virological studies have clearly demonstrated that specific human papillomavirus (HPV) types play a central role in the development of cervical cancer and its intraepithelial precursor lesions.

## HPV (Human PapillomaVirus)

- More than 115 HPV genotypes have been identified of which approximately 40 can infect the mucosa of the anogenital tract. Based on their etiological role in cervical carcinoma and its precursor lesions cervical intraepithelial neoplasia (CIN), HPV genotypes are classified into "high-risk" HPV (HR-HPV), "probable high-risk" HPV and "low-risk" HPV (LR-HPV) genotypes.



- The HR group includes 15 established HR-HPV genotypes (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) which have to be associated with cervical cancer, while the LR group includes 12 HPV genotypes (types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108) which are not potentially oncogenic and not involved in the development of cervical cancer. Three HPV genotypes (types 26, 53 and 66) are classified as probable high-risk genotypes.

- In the natural development of HPV, most infections are transient, especially among younger women; only a small

fraction of infections persist and may progress to cervical cancer, usually after more than a decade. Several studies have shown that women presenting a persistent infection with a HR-HPV genotype are at a significantly higher risk of developing high-grade dysplasia (CIN2/3)

- Because HPV DNA tests are more sensitive and have a higher negative predictive value (NPV) for CIN2 or worse (CIN2+) compared to cervical cytology, HPV DNA testing has been proposed to improve the efficacy of cervical carcinoma screening programs, particularly for the triage of women with ASC-US or LSIL cervical smears

## Cytological screening : The Pap Smear

- The current cornerstone for the detection of cervical cancer precursor lesions is the Papanicolaou-stained (Pap) cytological smear.

- Several cytology-based cervical cancer studies, which use the Pap smear and new cytological methods such as liquid-based cytology, have been implemented for the prevention of cervical cancer.

- Liquid-based cytology testing has been reported to increase the sensitivity of cervical cytology screening and the proportion of slides that are satisfactory for assessment, in comparison with conventional cytology.

- Despite this improvement, the sensitivity of the Pap Smear remains under 80%. Therefore, a global improvement of cervical cancer screening requires cytology and ancillary testing, such as the HPV DNA Test.

## HPV DNA test

- HPV cannot be reliably cultured in a laboratory setting; therefore, HPV diagnosis relies on molecular methods that detect HPV DNA in both endocervical samples and liquid-based cytology specimens. Different molecular methods are commercially available to screen a broad spectrum of HPV genotypes.

**HPV detection "in aggregate"**: Some molecular methods allow for simultaneous detection of the 13 HR-HPV genotypes using a liquid hybridization format (*Hybrid Capture*®2, Qiagen) or using a PCR-based method (*Amplicor*® HPV

Test, Roche Diagnostics). Recent commercial tests target the expression of viral transcripts (HPV mRNA) from different HR-HPV (*Aptima*® HPV test, Gen-Probe - *PreTect*™ HPV-Proofer test, Norchip - *NucliSENS EasyQ*® HPV, BioMérieux). All these methods allow us to simultaneously detect from 5 to 14 HR-HPV types but do not allow for the identification of individual HPV genotypes.

### ■ Full spectrum HPV genotyping assays

Newer HPV genotyping assays have been developed to identify individual HPV genotypes. The *INNO-LiPA HPV Genotyping Extra* test (Innogenetics) and the *LINEAR ARRAY*® HPV assay (Roche Diagnostics) are PCR-based HPV detection assays coupled with a reverse line blot hybridization on strip, which allows for the respective discrimination of 28 and 37 different HPV genotypes. The *Seeplex*™ HPV 18 Genotyping kit (Seegene) is a multiplex PCR using the dual priming oligonucleotide chemistry (DPO™) which detect 18 different HPV genotypes. Finally, different HPV DNA chips are commercially available such as the *PapilloCheck*® test (Greiner Bio-One) or the *CLART*® HPV 2 (Genomica) which allow for the detection of 24 and 35 different HPV genotypes respectively.

- The use of HPV genotyping assays that discriminate HPV16/18 from other HPV genotypes could be a promising approach for pre-vaccination screening and/or surveillance. Such a solution using real-time PCR methods is proposed by the *RealTime HR-HPV DNA test* (Abbott) or the future HPV test from Roche Diagnostics and by the *Cervista*™ HPV HR test (Hologic) based on the Invader® chemistry, which is an isothermal signal amplification system.

