

## VALGENT: Clinical Validation of Human Papillomavirus Genotyping Tests

**Object:** to discuss two questions on HPV genotyping

- 1) Can we use it in clinical practice?
- 2) If yes, what are acceptable assays?

**Short description:**

The use of HPV genotyping is established in assessment of the HPV vaccine efficacy in RCT, in surveillance of the effects of HPV vaccination, and epidemiological surveys. However, no consensus exists regarding its use in clinical practice and no criteria exist regarding the technical and clinical requirements. The VALGENT (clinical validation of HPV genotyping tests) provides a comprehensive design to validate and compare HPV genotyping assays.

Up to now four and six HPV assays were evaluated using as a standardised set of 1300 residual samples remnant after routine screening in Belgium and Scotland, respectively. VALGENT-3 and VALGENT-4 (using Slovenian and Danish samples) are being prepared.

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Thirteen high-risk Human Papillomavirus (hrHPV) types cause cervical cancer, the 3rd most incident cancer among women worldwide. General hrHPV assays such as the Hybrid-Capture II test and certain PCR systems, that detect DNA of hrHPV, can be used in triage of women with an equivocal Pap smear, in follow-up of women treated for cervical precancer and in primary cervical cancer screening. Consensus guidelines have been developed regarding the requirements of general hrHPV tests. Other HPV assays exist that allow distinguishing individual HPV types (genotyping). HPV genotyping is indicated in the evaluation of prophylactic HPV vaccines and in epidemiological studies. However, the utility of genotyping tests in clinical practice (screening or, management of screen-positive women) is not established. Moreover; the minimal requirements in terms of sensitivity & specificity, which a genotyping assay should fulfil to justify clinical use, remains undefined.

The VALGENT study aims: to define the potential role for HPV genotyping tests in clinical practice; to assess their accuracy in different clinical applications to detect cervical pre-cancer; and to develop a tool for evaluation and comparison of different HPV genotyping assays.

The VALGENT protocol consists in HPV genotyping with multiple assays of archived cervical cellular material remnant after routine cytological examination.

The study population is standardised: 1,000 continuous samples from women participating in screening enriched with 100 ASC-US, 100 LSIL and 100 HSIL samples.

The 300 pathological samples also come from the screening population and are also selected on a continuous basis to avoid selection bias and assure representativity.

Follow-up information is collected from the women whose samples are included in the study population and who are followed in agreement with current local guidelines. It is expected to find 90-130 CIN2+ cases and these samples are used to compute clinical sensitivity. Samples from women with a negative cytological result and having again a negative result at subsequent screening will be used to compute clinical specificity. A first panel of 1300 Belgian samples has been composed and genotyped with 4 assays and a second panel of Scottish samples. Six HPV genotyping tests were applied among which three were already used in VALGENT-1. Generation of more panels is considered. It is foreseen that at least one HPV assay is used that was already evaluated in a previous panel. HPV tests identifying cocktails of high-risk HPV types or tests identifying only a few types (HPV 16 and 18, for instance) can be included as well. This allows developing networks of test comparisons which can be pooled using MTM (multiple testing meta-analysis).

**Outputs:**

- comprehensive system for test validation and comparison
- listing of tests which fulfil minimal requirements
- development of a matrix of tests allowing translation of HPV prevalence studies from surveys using different tests.