

Genotyping of Human Papillomavirus Viruses Using Linear Array

April 2013

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1 GENERAL INFORMATION

1.1 Submitting company, institution or organization:

CHAUQ – Hôpital Saint-Sacrement [Saint-Sacrement Hospital, a branch of the Quebec City University Hospital Centre]

1.2 Application Submitted: November 29, 2011.

1.3 Notice Issued: April 2, 2013.

Note:

This notice is based on the scientific and commercial information [submitted by the requestor(s) and on a complementary review of the literature] according to the data available at the time that this test was assessed by INESSS.

2 TECHNOLOGY, COMPANY, AND LICENCE(S)

2.1 Name of the Technology

Roche LINEAR ARRAY HPV Genotyping Test kit for human papillomavirus.¹⁵

2.2 Brief Description of Technology

A qualitative *in vitro* test for determining the HPV genotype in clinical specimens, by use of PCR to amplify HPV DNA, followed by reverse hybridization on a nylon strip. Analyzer used: PCR thermocycler. The test can detect 37 different genotypes, including 13 that are high-risk (information taken from the completed application form).

2.3 Company or Developer: Roche Molecular Systems Inc.

2.4 Licence(s)

2.5 Patent, if Applicable

2.6 Approval Status (Health Canada, FDA)

Health Canada Licence No. 68149

Device class: 3

Date first issued: November 17, 2006

2.7 Weighted Value: 156.77 (Information Taken from the Completed Request Form).

¹⁵ <http://molecular.roche.com/assays/Pages/LINEARARRAYHPVGenotypingTest.aspx>

3 CLINICAL INDICATIONS, PRACTICE SETTINGS, AND TESTING PROCEDURES

3.1 Targeted Patients

Test used for assaying HPV in ENT carcinomas and for genotyping HPV in cervical biopsies and other formalin-fixed, paraffin-embedded (FFPE) specimens (information taken from the completed application form).

Other indications: In screening for cervical cancer in women 30 years and older who have had negative cytology but a positive HPV DNA test result for any of the 13 or 14 high-risk HPV genotypes, genotyping to detect HPV genotypes 16 and 18 can be clinically useful for identifying women who should be referred for colposcopy and those who should undergo a follow-up repeat cytology and HPV test after 12 months [ASCCP 2009].

3.2 Targeted Diseases

Human papilloma virus (HPV) is one of the most common sexually transmitted infections. The majority of persons infected are asymptomatic, and 90% will no longer have the infection after one or two years. For the remaining 10%, the infection will persist, and the risk of developing cancer will increase [Zandberg *et al.*, 2013]. Cervical cancer is the 13th most common cancer among Canadian women; in 2012, there were 280 new cases in Quebec and 1,350 in Canada as a whole [Canadian Cancer Society, 2012]. HPV infection is present in 99% of cervical cancer cases. This virus is believed to be the main cause of this cancer, and of a pre-cancerous lesion, cervical intraepithelial neoplasia (CIN, grades 1 to 3) [Roche 2010]. About 40 different genotypes of HPV can infect the human genital mucosa, but only 15 are regarded as at high risk of being associated with dysplasia or cervical cancer. A persistent infection by one of these types of HPV increases the risk of cancer, although several decades may pass between the initial infection and the development of cancer [INSPQ, 2011]. It is during this period that screening can detect cellular abnormalities that will call for closer monitoring or early treatment. HPV type 16 is believed to be responsible for 50% of these cancers, HPV 18 for 10% to 15%, HPV 45 for 7%, and HPV 31 for approximately 3% [Khan *et al.*, 2005]. Most genital HPV infections heal spontaneously, and the risk of cancer is associated solely with persistent infections. HPV 16 also appears to be associated with certain oropharyngeal cancers (head and neck squamous cell carcinoma) [Psyrris *et al.*, 2009].

3.3 Number of Patients to Be Tested

According to the requestor, the volume expected at CHA Saint-Sacrement (covering the territory of the RUIS Laval integrated university health network and eastern Quebec) is 180 tests per year. However, the requestor states that other Quebec hospitals offer the test, but are using another technology.

3.4 Medical Specialists Involved

Pathologists, gynecologists, ENT, oncologists, hematologist-oncologists.

3.5 Testing Procedure

Sample on a medium validated in an institution or in a physician's office. The method is described in detail in the company's product monograph [Roche 2010].

4 TECHNOLOGY BACKGROUND

4.1 Nature of the Diagnostic Technology: Complementary or "unique."

4.2 Brief Description of the Current Technological Context

No HPV genotyping test is available in the Quebec public health-care system.

The Roche Linear Array is licensed in Canada and in Europe, but not in the United States.

In April 2011, the FDA approved the Roches cobas 4800 HPV test, which is a quantitative test that can detect high-risk strains of HPV (using DNA amplification) and genotype HPV 16 and 18 simultaneously.¹⁶ This test was also licensed by Health Canada in April 2010.

Other methods of diagnosing HPV are available to test for the presence of DNA without genotyping (HC II).

4.3 Brief Description of the Advantages Cited for the New Technology

According to the requestor, this is a robust method that can be used to analyze several types of pathology specimens, including FFPE specimens, and to determine the precise HPV genotype present.

In general, HPV detection and genotyping tests increase the sensitivity of detection of high-grade lesions (CIN 2+) of the cervix and reduce the number of ambiguous Pap smear results that are referred for colposcopy. However, the inappropriate use of HPV testing also increases costs and can result in overtreatment [Twiggs *et al.*, 2011].

4.4 Cost of the Technology and the Options: Has not been analyzed.

5 EVIDENCE

5.1 Clinical Relevance (Utility and Validity) and Analytical Validity

5.1.1 Other Tests Replaced

None

5.1.2 Diagnostic or Prognostic Value

Mortality: a single recent study was found describing the effect of the type of HPV on survival of patients with adenocarcinoma of the uterine cervix [Baalbergen *et al.*, 2012]. This study concludes that in most cases (89%) the adenocarcinoma is related to HPV infection and that the most common type (54%) is HPV 18. However, except for HPV 45, HPV positivity has no impact on five-year survival.

Morbidity: No information

Survival: No information

¹⁶ http://www.roche.com/media/media_releases/med-cor-2011-04-20.htm

Quality of life: No information

Recurrence: N/A

Availability of a treatment: N/A

Changes in treatment because of the results of the test: stated usefulness for stratifying HPV-positive women according to their risk of pre-cancerous lesions or cancer to determine the best clinical strategy [Meijer *et al.*, 2006].

One study reports that in head and neck squamous cell cancers, the recommended treatment for HPV-positive patients is the same as for “conventional” cases. The usefulness of the test would be limited to stratification of patients in clinical trials with the goal of possibly finding less aggressive treatments [Black *et al.*, 2010].

Adverse effects: improper use of genotyping tests can result in too many colposcopies and overtreatment. These effects will be greater if the tests used are not correctly validated [Meijer *et al.*, 2006].

5.1.3 Therapeutic Value

In general, the studies mention three clinical applications for HPV genotyping in cervical cancer: 1) triaging women with atypical cytology, ASCUS, or low-grade squamous intraepithelial lesions (LSIL); 2) monitoring women for prognostic purposes after treatment of high-grade lesions; and 3) screening women for cervical cancer (see recommendations below).

5.2 Clinical Validity

Component	Presence	Absence	Not Applicable
Sensitivity	x		
Specificity	x		
Positive predictive value (PPV)	x		
Negative predictive value (NPV)	x		
Likelihood ratio (LR)		x	
ROC curve	x		
Accuracy		x	

Sensitivity (Se): Generally high (> 90%) and higher in high-grade cases (CIN 2+) and when compared with the results of cytology, histopathology, and other diagnostic procedures.

A recent meta-analysis [Arbyn *et al.*, 2012] of nine studies indicates an Se of 93.8% (90.2% to 97.5%) for the Linear Array test for triaging women with ASCUS and 99% (97.7% to 100%) for women with LSIL, for the purpose of finding CIN 2+ lesions. The relative Se, compared with the HC II test (Hybrid Capture, a test for detection of DNA without genotyping) is not significant (1.02%; 0.99% to 1.06%) (five studies).

The product monograph from the manufacturer (Roche) reports a clinical Se of 96% (92% to 98%) for 689 clinical cervical specimens, for high-risk HPVs tested with HC II.

Specificity (Sp): 24.8% to 51.7%, according to the studies.

The meta-analysis by Arbyn *et al.* [2012] of nine studies indicates that the Linear Array test has an Sp of 46.2% (37.9% to 54.5%) for triaging women with ASCUS and 28.1% (22.5% to 33.6%) for women with LSIL, for the purpose of finding CIN 2+ lesions. The Linear Array test's relative Sp, compared with the HC II (Hybrid Capture) test is not significant (1.00%; 0.96% to 1.04%) (five studies).

The monograph from the manufacturer (Roche) reports a clinical Sp of 99% (98% to 100%) for 689 clinical cervical specimens, for high-risk HPVs tested with HC II.

Positive predictive value (PPV): Fairly high (73.6%) in the study by Tabrizi *et al.* [2012]; it is also highly variable and generally < 30%, especially for high-grade lesions (CIN 2+).

Negative predictive value (NPV): 80.8% to 100%.

Likelihood ratio (LR): Not specified in the reviewed studies.

ROC curve: Area under curve is 0.55 to 0.67.

Accuracy: Not calculated.

5.3 Analytical (Technical) Validity

Component	Presence	Absence	Not Applicable
Reproducibility/Repeatability	x		
Analytical sensitivity		x	
Analytical specificity		x	
Matrix effect		x	
Concordance	x		
Correlation		x	
Other, according to type of test			

Reproducibility/repeatability: The manufacturer's monograph reports that reproducibility was tested on 451 clinical specimens, with 3 batches of reagents, 5 combinations of instruments, and 3 different operators, on a total of 15 series. No variability was detected from one instrument, operator, batch, or series to another.

Matrix effect: No information.

Concordance: Variable results based on comparisons with other diagnostic methods. Here we give the results of the Linear Array compared with laboratory controls.

According to Steinau *et al.* [2012], concordance with the control plasmid (66 samples) is 98.7% (kappa 0.992).

Correlation coefficient: No information.

Cross-reactions: The manufacturer's monograph reports that there was no cross-reactivity with a variety of viruses, bacteria, protozoa, and yeasts that may be present in cervical specimens.

Detection limit: HPV 16, 200 cells/mL and HPV 18, 1,300 cells/mL (manufacturer's monograph).

5.4 Recommendations for Listing in Other Jurisdictions

Indication in the case of **screening for cervical cancer**: In women 30 years and older who have had a negative cytology result but a positive HPV DNA test result for any of the 13 or 14 types of HPV that are considered high-risk, genotyping to detect HPV 16 and 18 is recommended. If the genotyping is positive, the women should be referred for colposcopy; if it is negative, a 12-month follow-up should test for cytology and HPV [Saslow *et al.*, 2012; ASCCP 2009]. No specific genotyping test is recommended.

In Quebec, screening for cervical cancer is opportunistic. In its 2011 report, the INSPQ [Quebec Institute for Public Health] recommended cytological testing (using either a conventional smear or the liquid-based method) for all women who are or ever have ever been sexually active. Among other things, the report recommends that beginning at the age of 30, women with ambiguous ASCUS screening test results should be referred for an oncogenic HPV DNA detection test. If the result of that test is positive, they should be referred to colposcopy; if it is negative, the cytological test should be repeated 12 months later [INSPQ 2011].

The Canadian recommendations on screening for cervical cancer, published in January 2013, do not address the question of HPV testing, given the limited evidence on how these tests affect invasive cancer incidence and mortality rates. This recommendation will be revised when data become available [Canadian Task Force on Preventive Health Care, 2013].

No guideline was found regarding the clinical application of this test for purposes other than cervical cancer screening.

6 EXPECTED OUTCOME OF INTRODUCING THIS TEST

6.1 Impact on Human and Material Resources: Not analyzed.

6.2 Economic Impact of Including this Test in the Health and Social Services System: Not analyzed.

6.3 Main Organizational, Ethical, Social, Legal, and Political Issues: Not analyzed.

7 INESSS NOTICE IN BRIEF

Genotyping of HPV Viruses Using the Roche Linear Array Kit

Status of the diagnostic technology

Established (in terms of technical validity)

Innovative

Experimental (for research only)

Replacement for technology: _____, *which is becoming obsolete.*

INESSS recommendation

Include in the Index

Do not include in the Index for the indication shown in the application (assaying HPV in ENT carcinomas and in cervical biopsies and other formalin-fixed, paraffin-embedded specimens).

Evidence of the clinical utility of this test is not available for this indication.

Reassess

INESSS decision regarding any required work

Draw connection with listing of drugs, if it is a companion test.

Produce an optimal use manual.

Produce indicators, if close monitoring is required.

None.

NOTE: This test could, however, be useful from a public health standpoint (monitoring in a context of universal vaccination) or in research projects.

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