GeneCell Diagnostics HPV E6E7 mRNA Set-up Project 2014-15

“We believe that if you show the people the solution to their hidden problems, they will be moved to ACT!”

HPV OncoTect® has moved clinical opinion in USA, Canada, South America & Europe. Now in India too.

Tel +91 11 2646 2636
Fax +91 11 4105 5709
234A, Chandi Plaza, Sant Nagar, East of Kailash, New Delhi- 110065.
India
www.genecell.in
hpvtest@genecell.in
# Contents

About Cervical Cancer Prevention & Control .................................................. 1  
About the Test – HPV OncoTect E6E7 mRNA Test ........................................ 3  
Why HPV mRNA Test? Key Clinical Evidences ............................................... 6  
Intracellular human papillomavirus E6, E7 mRNA quantification predicts CIN 2+ in cervical biopsies better than Papanicolaou screening for women regardless of age. ............................................................... 6  
Human papillomavirus E6/E7 mRNA testing as a predictive marker for cervical carcinoma. ................................................................. 8  
Clinical performance of human papillomavirus E6 and E7 mRNA testing for high-grade lesions of the cervix. ................................................................. 9  
Human papillomavirus genotyping and e6/e7 mRNA expression in greek women with intraepithelial neoplasia and squamous cell carcinoma of the vagina and vulva. ............................................................... 11  
Human papillomavirus (HPV) E6/E7 mRNA as a triage test after detection of HPV 16 and HPV 18 DNA. ................................................................. 12  
HPV OncoTect setting up Proposal ............................................................... 16  
Clinical Justification .................................................................................. 23  
Global Users & Their Gains ....................................................................... 24  
Contact Information .................................................................................. 31  
Company Information .................................................................................. 31

(Please use Ctrl + Click to follow page number links to the section text)
About Cervical Cancer Prevention & Control

Strategic Highlights
Testing for HPV DNA provides a very good approach to screening a population for cervical precancer owing to its superior negative predictive value (NPV). But it lacks clinical specificity and hence positive disease prediction (PPV) that enables clinicians to identify a symptomatic woman to be correctly detected for cervical or lower genital abnormalities due to high risk HPV. The OncoTect just fills up this void that is unmatched by any other test currently. It has equal if not higher sensitivity as well as high specificity that correlates well with colposcopic diagnosis of high grade lesion. It is the only quantitative HPV test that detects over-expression of viral oncogenic activity that triggers cellular changes leading to CIN.

Financial Highlights
Owing to better NPV, a negative HPV DNA test eliminates future risk and anxiety for cervical cancer but helps too little for women presented with lower genital or lower abdominal pains to ascertain their current risk for offering the appropriate management or treatment options. As a result, a diagnostic algorithm that relies only on HPV DNA remains multi-layered and expensive with an additional risk of losing the patients for follow up. HPV mRNA, due to its highest PPV identifies disease status correctly and saves money for a patient in seeking second opinion or losing them for follow up.

Operating Highlights
The HPV OncoTect is the only quantitative, intact cell based molecular in situ hybridization test that combines the superior power of flow cytometry in
detecting a quality and quantity of HPV oncogenes over-expressing so as to cause cellular transformation leading to cervical cancer. This is a path-breaking non-PCR technology that allows biological samples to be processed without having to isolate and purify DNA or RNA, making the technology highly reproducible.

**Looking Ahead**

The flow cytometry based proprietary molecular hybridization technology allow us to introduce a multiplexed Sexually Transmittable Infections’ panel as well as a unique screening test for breast cancer detection by incorporating ER+/-, PR+/-, HER 2 neu+/-, E-Cadherin and DNA Ploidy to be offered to the oncopathology profile to the niche pathology labs in India.

In addition to preclinical detection, Incelldx’s assay has multiple applications for use:

- As a companion diagnostic for current HER2/ER/PR therapies like Herceptin and Tamoxifen.
- In xenograft model cell analysis
- In circulating tumor cell detection on whole blood.

**Discussion Breast Cancer Screening...**

- Current methods of breast cancer detection rely on mammography, PSA/suspension, and IHC/FISH.
- Clinically detectable breast cancer by mammography is routinely found at a tumor size of 1 cm and greater.
- At that point, the tumor has been present and growing for 7-10 years with a great chance of metastatic spread having already occurred.

**Years before other tests could detect Br Ca**

- Our combinatorial assay on breast tumors has the potential to fulfill that early step missing in current breast cancer detection.
About the Test – HPV OncoTect E6E7 mRNA Test

The OncoTect® Test is the only commercially validated clinical diagnostic kit for human papillomavirus for HPV E6/E7 mRNA over-expression quantitative testing, manufactured by IncellDx, USA. It is a sensitive flow cytometry based assay that utilizes molecular in situ hybridization and quantitatively detects over-expression of HPV E6, E7 mRNA in intact human cells. This technique has been reported to have clinical sensitivity at par with the other established commercially validated and widely documented HC2 assay (Qiagen, USA) but manifold better clinical specificity than any other molecular assays so far available for primary screening and triaging of high grade cervical precursor lesions (CIN2+) and is designed to be used with other established methodologies as an indicator of active or replicative precursor disease activity (CIN). Cervical specimens to be collected in the conventional liquid based cytology (LBC) media such as PreservCyt or SurePath or LiquiPrep are suitable to be processed for HPV E6/E7 mRNA detection by OncoTect®.

Current investigations suggest active viral E6/E7 gene mRNA expression precedes or coincides with morphologic changes in cervical cells signifying precursor lesions those progresses to cervical cancer. Unlike HPV DNA testing, E6/E7 mRNA detection allows the identification of transcription active viruses. During carcinogenesis, integration of viral DNA occurs into the host cell genome, causing a disruption of the E2 open reading frame, and thus leading to an up-regulation of the viral oncogenes E6 and E7. The E6/E7 proteins inactivate growth inhibitors within the cell, most importantly the tumor suppressors, p53 and pRB. Overexpression of these oncoproteins is a trigger event for an increased risk of cervical cancer. E6/E7 oncogenic expression can be detected by testing for E6/E7 mRNA transcripts within the cells of the diseased patients.
About the Test – HPV OncoTect E6E7 mRNA Test

This procedure adopts clinical performance of the E6/E7 mRNA-based HPV test, the HPV OncoTect (IncellDx, CA, USA), on the residual or fresh material collected for LBC. The results of the HPV OncoTect® are highly correlated with histopathologic CIN2+ as a clinical end-point on the colposcopically directed tissue specimen.

Cervical cancer has been linked to HPV infection and in particular, oncogenic serotypes of HPV. Genotypic DNA is encoded in the L1 gene region that expresses the major capsid proteins during the late phase of viral life cycle. Detection of oncogenic serotypes of HPV has been done by a variety of solution-based techniques. Most of these techniques have in common the destruction of cells containing HPV, isolation and purification of total DNA, and detection of serotype-specific HPV DNA sequences (L1). The techniques used for detection include predominantly polymerase chain reaction (PCR), HC2® based on solution hybridization, and Southern Blot. All of these techniques involve destruction of cells, detection of HPV DNA, and detection of L1 gene sequences in common with all oncogenic HPV types or full length viral genome hybridization for group serotype specificity.

The HPV OncoTect® E6, E7 mRNA test utilizes a different approach to detect viral infection, including a different selection strategy for oncogenic serotypes, different detection methodology, and a different HPV gene target (mRNA).

The OncoTect determines the clinical sensitivity and specificity in the hospital visiting symptomatic population in comparison for follow up for histopathologic confirmation of CIN2 and CIN3 for women positive by either of the tests. This information is very useful in the prognosis of women of any age and particularly young women of 30 years or under, to correctly detect and manage women with precancer lesions whereas the existing clinical guidelines provide diagnostic algorithm for women above 30 years of age that follows multi-layered triaging procedures for abnormal lesions.
4.1 METHODOLOGY

The OncoTect® HPV E6/E7 mRNA assay utilizes a different intact cell analysis approach to detecting the integrated form of the viral infection more aggressively associated with CIN than a non-integrated episomal viral DNA that is abundantly prevalent amongst the sexually active women. It targets a different HPV gene target (mRNA).

The use of the OncoTect® HPV E6/E7 mRNA Assay is clinically indicated,

- to screen women with ASC-US cervical cytology results to determine the need for referral to colposcopy.
- the OncoTect® HPV E6/E7 mRNA Assay test can be used in conjunction with Visual Inspection with Acetic acid (VIA) or Lugol’s Iodine (VILI) and/or cervical cytology to assess the presence or absence of oncogenesis trigger. This information, together with the patient's cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

The HPV OncoTect® technique involves five (5) simple steps, starting with physiological specimen without sample pre-treatment:

- CELLULAR PREPARATION.
- CELL FIXATION AND PERMEABILIZATION.
- HYBRIDIZATION.
- WASH
- ANALYSIS

Following cellular preparation (which may include surface antigen labeling), the cells are fixed and permeabilized in a one-step reaction, hybridized with an oligonucleotide probe cocktail, washed to remove unbound probe, and analyzed by flow cytometry.
Why HPV mRNA Test? Key Clinical Evidences


Intracellular human papillomavirus E6, E7 mRNA quantification predicts CIN 2+ in cervical biopsies better than Papanicolaou screening for women regardless of age.

Pierry D, Weiss G, Lack B, Chen V, Fusco J.
Clinical Pathology Department, Hunter Laboratories Inc, Campbell, CA 95008, USA. dpierry@hunterlabs.com

Abstract

CONTEXT:
Cervical cancer screening in women younger than 30 years relies on cervical cytology because of the poor performance of human papillomavirus (HPV) DNA testing in this age group.

OBJECTIVES:
To determine the performance of in-cell HPV E6, E7 mRNA quantification (HPV OncoTect) for the detection of high-grade cervical intraepithelial neoplasia in women younger than 30 years.

DESIGN:
We analyzed 3133 cytology specimens from a screening population of women aged 19-75 years investigate HPV OncoTect as a triage/secondary screening test for atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) cytology in women younger than 30 years. Test results were compared to histology in 246 cases.

RESULTS:
The sensitivity of E6, E7 mRNA was 89% for CIN 2+ and 100% for CIN 3+ lesions in women 30 years and older. In women younger than 30 years, the sensitivity of E6, E7 mRNA for CIN 2+ lesions was 88% for CIN 2+ and 92% for CIN 3+ lesions. Abnormal cytology (≥ASCUS) exhibited a sensitivity of 89% for CIN 2+ and 100% for CIN 3+ in women 30 years and older and 96% sensitivity for CIN 2+ and 93% sensitivity for CIN 3+ in women younger than 30. The specificity of E6, E7 mRNA was >80% for CIN 2+ and CIN 3+ in both groups of women compared to a specificity of abnormal cytology of <10% for CIN 2+ and CIN 3+ in both groups.

**CONCLUSIONS:**

HPV OncoTect demonstrates a performance that would be effective for ASCUS/LSIL triage in women including those younger than 30 years.
Human papillomavirus E6/E7 mRNA testing as a predictive marker for cervical carcinoma.

Lie AK, Kristensen G.
Department of Pathology, The Norwegian Radium Hospital, Rikshospitalet, N-0310 Oslo, Norway. akl@radiumhospitalet.no

Abstract

Human papillomavirus (HPV) is necessary for the development of cervical carcinoma, and incorporation of molecular testing for HPV in screening and patient management has been proposed. Sufficient scientific evidence exists to recommend HPV DNA testing in the triage of women with equivocal cytology and in follow-up after the treatment of precursor lesions. However, due to a low clinical specificity and positive predictive value, HPV DNA testing has so far not been recommended as primary screening in Europe. In general, diagnostic HPV tests have to demonstrate accuracy, reproducibility and clinical utility before they can be used in patient management and implemented in cervical cancer screening programmes. In this article we give an overview of RNA-based HPV diagnostics and the role of E6/E7 mRNA detection as a predictive marker for the development of cervical carcinoma. HPV E6/E7 mRNA testing for high-risk types seems to correlate better with the severity of the lesion compared with HPV DNA testing, and is a potential marker for the identification of women at risk of developing cervical carcinoma. Commercial assays for simultaneous genotyping and detection of E6/E7 mRNA from the five most common high-risk HPV types are now available.
Clinical performance of human papillomavirus E6 and E7 mRNA testing for high-grade lesions of the cervix.


Institute of Microbiology, Università Cattolica del Sacro Cuore, Largo A Gemelli 8, Rome 00168, Italy. pcattani@rm.unicatt.it

Abstract

Infection with high-risk (HR) human papillomavirus (HPV) is the major cause of cervical cancer. However, relatively few infections progress to malignant disease. Progression to malignancy requires the overexpression of the E6 and E7 genes in the integrated HPV genome. It follows that the E6 and E7 transcripts could be useful markers of disease progression. The study presented here tests this possibility, using data from colposcopy and from cytological and histological tests to compare RNA assays for the E6 and E7 genes with DNA testing. A total of 180 women underwent colposcopy, cytology, and biopsy of suspected lesions (143 cases). Cervical brush specimens were analyzed for HPV DNA and for E6 and E7 mRNA. DNA from HR HPV was found in 57.8% of the specimens; E6 and E7 transcripts were found in 45%. The rates of detection of HPV DNA and of E6 and E7 transcripts were 33.3% and 25%, respectively, for specimens with normal findings; 51.4% and 31.9%, respectively, for specimens with cervical intraepithelial neoplasia grade 1 (CIN1); and 61.1% and 44.2% for specimens with CIN2, respectively. All specimens with CIN3 and 95.5% of specimens from patients with squamous cell carcinoma were positive by both assays. Thirty-seven patients with normal colposcopy findings did not undergo biopsy. HPV DNA and mRNA transcripts were found in 32.4% and 18.9% of these cases, respectively. Comparisons with cytological tests produced similar results. Overall, the mRNA tests showed a higher specificity than the DNA tests for high-grade lesions (72.7% and 56.2%, respectively) and a higher positive predictive
value (59.3% and 49.0%, respectively). These findings suggest that mRNA assays could be more powerful than DNA testing for predicting the risk of progression and offer a strong potential as a tool for triage and patient follow-up.
Why HPV mRNA Test? Key Clinical Evidences


Human papillomavirus genotyping and e6/e7 mRNA expression in greek women with intraepithelial neoplasia and squamous cell carcinoma of the vagina and vulva.

Tsimplaki E, Argyri E, Michala L, Kouvousi M, Apostolaki A, Magiakos G, Papassideri I, Panotopoulou E.

Department of Virology, “G. Papanicolaou” Research Center of Oncology and Experimental Surgery, Regional Anticancer Oncology Hospital of Athens “St. Savvas”, 171 Alexandras Avenue, 11522 Athens, Greece.

Abstract

A large proportion of vaginal and vulvar squamous cell carcinomas (SCCs) and intraepithelial neoplasias (VAIN and VIN) are associated with HPV infection, mainly type 16. The purpose of this study was to identify HPV genotypes, as well as E6/E7 mRNA expression of high-risk HPVs (16, 18, 31, 33, and 45) in 56 histology samples of VAIN, VIN, vaginal, and vulvar SCCs. HPV was identified in 56% of VAIN and 50% of vaginal SCCs, 71.4% of VIN and 50% of vulvar SCCs. E6/E7 mRNA expression was found in one-third of VAIN and in all vaginal SCCs, 42.9% of VIN and 83.3% of vulvar SCCs. Our data indicated that HPV 16 was the commonest genotype identified in VAIN and VIN and the only genotype found in SCCs of the vagina and vulva. These findings may suggest, in accordance with other studies, that mRNA assay might be useful in triaging lesions with increased risk of progression to cancer.
Why HPV mRNA Test? Key Clinical Evidences


**Human papillomavirus (HPV) E6/E7 mRNA as a triage test after detection of HPV 16 and HPV 18 DNA.**


Department of Microbiology, University Hospital of Vigo, Vigo, Spain. sonia.perez.castro@sergas.es

**Abstract**

High-risk human papillomavirus (HPV) DNA detection provides high sensitivity but low specificity for moderate-grade cervical intraepithelial neoplasia or worse histological identification. A prospective study evaluated mRNA testing efficacy for predicting this histological diagnosis in case of HPV 16 and/or 18 DNA detection. A total of 165 endocervical samples harboring HPV 16 and/or 18 DNA were tested with HPV E6/E7-mRNA-assay. Women with cytological alterations were referred to colposcopy (n = 111). Moderate-grade cervical intraepithelial neoplasia or worse was diagnosed in 25.8% of women presenting atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions and in 89.8% of women with high-grade squamous intraepithelial lesions. mRNA sensitivity was 81.3% and 84.1%, respectively. Specificity was 52.2%, and 80.0%, respectively. Negative predictive value (NPV) was 88.9% in undetermined or low-grade squamous lesions. Positive predictive value (PPV) was 97.4% in high-grade squamous lesions. mRNA reduced colposcopies by 44.3% in undetermined or low-grade squamous lesions. Direct treatment of mRNA-positive cases reduced 77.5% of colposcopies in high-grade squamous lesions. Women without cytological alterations were followed for 18 months (n = 35), and moderate-grade cervical intraepithelial neoplasia or worse was diagnosed in 34.3%; mRNA sensitivity and specificity were 83.3% and 86.9%, respectively. PPV and NPV were 76.9% and 90.9%, respectively for
Why HPV mRNA Test? Key Clinical Evidences

predicting moderate-grade cervical intraepithelial neoplasia or worse in 18 months. mRNA reduced the number of visits for follow-up in 62.2%. In conclusion, HPV E6/E7-mRNA-assay can serve as a triage test in case of HPV 16 and/or 18 DNA detection.
Why HPV mRNA Test? Key Clinical Evidences

A big challenge for clinical diagnostic players to participate in global trials on new-gen mRNA target therapies..

mRNA Therapeutics Gain Momentum

Thu, 10/31/2013 - 9:45am Andrew S. Wiecek, Editor

A growing number of researchers are reinventing gene therapy with mRNA and finding success in treating cancer as well as other diseases. (Source: CureVac). It was a pleasant surprise when the first International mRNA Health Conference, which was held last week at the University of Tübingen in Germany, attracted more than 120 experts.

“A lot of pharma guys were there as well, from Pfizer, Sanofi and Takeda,” says Hoerr who was one of speakers at the event and is the CEO and co-founder of CureVac, a biopharmaceutical company that is developing mRNA vaccines. “It was quite interesting to see that there is awareness in pharma about this new technology.”

During the 1990s, studies discovered that when you placed RNA into the skin, the skin cells began to express the encoded proteins. That was really unexpected because everyone thought that RNA was unstable. Everyone was hesitant to work with RNA at the time. Instead, most researchers were focused on developing gene therapy using DNA molecules, which eventually ran into significant roadblocks and never lived up to its potential.

But Hoerr’s group found that RNA was actually quite stable when not in the presence of RNases that quickly degrade the RNA molecules. The molecule is so stable, in fact, that it can be kept at room temperature for at least two years without experiencing significant degradation.
A clear division in the application of this technology is evident. Some are using the technology to illicit an immune response. In this strategy, antigen-encoding mRNA are injected into the patient’s body, and then the patient’s cells take up the mRNA, express it and produce an immune response against the disease. In CureVac’s early cancer trials, over 80 percent of patients treated with their mRNA vaccines have had a specific immune response against their tumors, increasing the median survival rate from 15 to 30 months. These studies are much too small, and not controlled, to be a proof-of-concept, but it’s an indication that something right is happening.
HPV OncoTect setting up Proposal

Opportunity
Niche business opportunity in women’s health, with a promise of minimum 25% CAGR

Exclusivity
Exclusive identity for relatively small players in the Indian Healthcare Industry, vis-à-vis major players in the market.

Expanded Offerings
Adding on soon, the SEXUALLY TRANSMITTABLE INFECTIONS (STIs) multiplexing parameters. A single test is sufficient to screen most common STIs in the Indian scenario. Further, adding up a unique path-breaking BREAST CANCER screen.

Contingent Competition
The HPV DNA market is dominant with age-old hc2 or traditional, non-standardized, ill-reproducible home brew PCR or commercially available but very expensive PCR tests which do not much add-on to the emerging knowledge for the clinicians. HPV OncoTect thus faces no competition and provides most updated clinical knowledge about actual oncogenesis process that helps clinician manage or treat.

Takeaways
Firm grip on the Indian gynaecological oncology market segment. We are seen as the Industry leaders, setting up new Industry standards.
LABORATORY REQUIREMENTS for Setting up HPV ONCOTECT

LOCATION: The area of the Laboratory to perform HPV OncoTect could be a normal airconditioned lab area separate from the location where nucleic acid extractions for PCR are performed, if the condition applies. The OncoTect results may largely be unaffected but for sensitive PCR reactions.

SPACE:

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>MINIMUM SPACE REQUIRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow Cytometer</td>
<td>1 linear meter</td>
</tr>
<tr>
<td>Wet Lab workspace for assay performance</td>
<td>2 linear meters</td>
</tr>
<tr>
<td>Centrifuge, Heater Incubator/ Water Bath</td>
<td>0.25 linear meter</td>
</tr>
<tr>
<td>Plate Washing and draining area near a sink</td>
<td>0.5 linear meter</td>
</tr>
</tbody>
</table>
**FLOW CYTOMETER SPECIFICATIONS:**

<table>
<thead>
<tr>
<th>BENCH TOP FLOW CYTOMETER</th>
<th>SPECIFICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested makes:</td>
<td></td>
</tr>
<tr>
<td>1. BD Accuri C6</td>
<td><strong>Power Requirements</strong></td>
</tr>
<tr>
<td>2. Amnis FlowCyte</td>
<td>Voltage 230V, Power 25V, Frequency 50Hz</td>
</tr>
<tr>
<td>3. Beckman Coulter</td>
<td>Line Voltage Variation +/- 10%</td>
</tr>
<tr>
<td>Cytomics FC500</td>
<td>Line Frequency Variation +/- 3Hz</td>
</tr>
<tr>
<td></td>
<td><strong>Performance</strong></td>
</tr>
<tr>
<td></td>
<td>Dual Laser: 488 Excitation, 6 detector including forward and side scatter detectors.</td>
</tr>
<tr>
<td></td>
<td>FL1: 533±15nm (FITC/GFP)</td>
</tr>
<tr>
<td></td>
<td>FL2: 585±20nm (PE/PI)</td>
</tr>
<tr>
<td></td>
<td>FL3: &gt;670nm (PerCP-Cy5.5, PE-Cy5, PE-Cy7)</td>
</tr>
<tr>
<td></td>
<td>640 Excitation: As above plus: FL4: 675+12.5 nm (APC)</td>
</tr>
<tr>
<td>PC System supplied with Flow Cytometer</td>
<td></td>
</tr>
<tr>
<td>Printer</td>
<td>Inkjet, or equivalent</td>
</tr>
<tr>
<td>Software: IncellDx CFlow or IncellDx CFlow Plus</td>
<td>Windows 2008</td>
</tr>
<tr>
<td></td>
<td>MS Office 2007</td>
</tr>
<tr>
<td></td>
<td>OncoTect Specific Analysis</td>
</tr>
<tr>
<td></td>
<td>Software will be provided by GeneCell FOC</td>
</tr>
</tbody>
</table>

**ENVIRONMENT:** The laboratory should be clean, uncluttered and temperature controlled.

-The laboratory must have an adequate and stabilized electrical supply available for a Flow Cytometer, computer and accessories, centrifuge and water bath.
- The laboratory must have access to good quality, de-ionised or double distilled water
- The laboratory must have adequate 2-8°C storage for clinical specimens
- The lab area should be free of direct sunlight

MANPOWER: The laboratory must have at least TWO qualified personnel, ancillary lab equipment and work space to allow for the OncoTect to be run in accordance with manufacturer’s recommendations on good laboratory practice (GLP).

ADDITIONAL EQUIPMENT & MATERIALS REQUIRED

- 45 ± 2°C Water Bath or Incubator.
- Low temperature Centrifuge with a maximum speed of 10,000g.
- Vortex Mixer with cup attachment
- Single channel micropipettor and an 8-channel pipettor, 20 to 200 µl, and normal as well as aerosol-barrier tips.
- Repeating positive displacement pipettor (Eppendorf® or equivalent) and disposable syringe-type tips.
- Disposable bench covers, paper towels, powder-free gloves, and lint-free tissues
- Sodium hypochlorite solution (household bleach)
- Kimtowels® Wipers or equivalent (lint free tissue)
- Powder-free gloves
- 2-8°C refrigerator and -20°C freezer
- 5 ml serological pipettes
- 2 ml polypropylene tubes

It is required that ALL equipment units are operated only from power outlets with a LINE STABILIZER and High Voltage Surge Control to minimise or avoid damage due to high or low voltage power spikes beyond 190-240 volts.
THE KIT PRICING

- The HPV OncoTect kit pricing.

<table>
<thead>
<tr>
<th>CAT. NO.</th>
<th>DESCRIPTION</th>
<th>PRICE (₹) PER KIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>C12100</td>
<td>Kit includes all reagents and FL-labeled HPV probes (100-Test Kit)</td>
<td>198,000.00</td>
</tr>
<tr>
<td>Controls</td>
<td>Positive and Negative Control Cells in LBC preservative</td>
<td>25,000.00</td>
</tr>
</tbody>
</table>

PRODUCT DESIGN FEATURES

- **Analytical Sensitivity** 5-10 E6, E7 mRNA copies per cell
- **Clinical Decision Point** 2% of cells expressing
- **Specimens** LiquiPrep®, ThinPrep®, SurePath™
- **Specimen Adequacy Control** Quantification of minimum level of endocervical cells and cells per microliter (FSC versus SSC)
- **External Controls** Preserved cell lines well characterized as positive or negative
- **Result Interpretation** Positive or Negative, based on clinical decision cut-off
- **Input Volume** 500 μL
BUSINESS TERMS:

1. **Validity**: Offer Valid for the calendar year 2014.

2. **Marketing Support**: GeneCell assumes to carry out marketing campaign to promote conceptual HPV mRNA, STI test panel among Gynaecologists, Oncologists, STD, NGOs through seminars, CME participation etc as organized or as suggested by client lab time to time as prior mutually agreed, the cost-sharing of which will also be agreed mutually from event-to-event.

3. **Purchase Orders**: A client laboratory shall order kits by written purchase order to GeneCell Diagnostics P Ltd specifying number of units and desired schedule of supply.
4. **Payment Terms**: GeneCell Diagnostics P Ltd offers payment terms on accounts up to “30 days of credit” only from the date of Invoice, on purchase of kits and reagents.

5. **Supplies**: GeneCell Diagnostics P Ltd will arrange supply the products within maximum period of 4 weeks from the date of order confirmation, unless otherwise confirmed by GeneCell Diagnostics P Ltd. in writing.

6. **Taxes**: The prices quoted are exclusive of CST/ VAT/Octroi Duty which will be as applicable.

Make all PAYMENTS in favor of GeneCell Diagnostics P Ltd, New Delhi. If you have any questions concerning this, call: Dr Dinesh Gupta +91 103 14638 or Mr Pankaj Bhatia +91 103 55709 or Mr Pradeep Sharma +99710 99982.
Clinical Justification

“...The oncogenic role of HPV E6 & E7 oncogenes was long known to us since late 80’s and had been a topic of intense research. While HPV DNA created a strong footprint on cervical cancer screening segment, it did not add up required significance to detect women who carried the precursor lesions currently. Hence, its diagnostic utility remained limited.

With the advent of HPV E6/E7 mRNA Test, the HPV OncoTect, the current disease prediction is substantially enhanced, due to the fact that it is the only quantitative test in the world that deciphers real time oncogenic activity of the high risk HPVs that relates to high grade disease detection.”
Global Users & Their Gains

Why detect cervical cancer risk, when you can detect the early development of cervical cancer itself?

Introducing the new HPV OncoTect
NEW YORK, NY, June 10, 2011 – Enzo Biochem Inc. (NYSE: ENZ), as part of its continuing program to offer novel molecular tests, announced that its Enzo Clinical Labs subsidiary has reached an agreement with InCellDx Inc. of Menlo Park, CA, for the rights to market a proprietary laboratory test. The test is based upon HPV Oncotect™, an advanced molecular diagnostic technology for quantifying specific biomarkers that have been associated with an increased risk of progression to cervical cancer and will further expand Enzo’s approach to providing comprehensive clinical information to physicians for managing diseases associated with women’s health. Upon receiving the appropriate approvals, Enzo will become the first New York licensed reference laboratory to offer the test.

HPV Oncotect™ is a novel method for screening for the likelihood of progression to cervical carcinoma by measuring potential oncogenic activity of the human papillomavirus (HPV) in infected cervical cells. The assay functions by detecting and quantifying the expression of viral oncogenes responsible for triggering progression to cervical cancer, thus improving the specificity that existing tests lack. As with other assays developed at Enzo Clinical Labs, HPV Oncotect™ will be validated during in-house studies prior to seeking New York State approval under a “LDT” regulatory pathway. Favorable reimbursement already exists for this type of testing.

“The HPV Oncotect™ technology is a flow-cytometry based method that can be used to identify the genetic expression of HPV that has already integrated into the cell, offering a better indicator of serious HPV infections than can be accomplished by identifying the presence of the virus alone,” said Dr. Robert Boorstein, MD, PhD., Medical Director of Enzo Clinical Labs. "This addition to our growing line of molecular diagnostic tests for women’s health underscores our expanding specialization in advanced clinical and diagnostic testing. We intend to use this test initially for patients who have been shown to be HPV positive by standard techniques.”

HPV is one of the most common sexually transmitted diseases and is the major cause of cervical cancer. Published consensus guidelines recommend high risk HPV
Global Users & Their Gains

GenCerv: Quantifies the expression of HPV E6E7 mRNA

95% of women who tested positive for High Risk HPV do not progress to Cervical Cancer. GenCerv can help you identify the 5% who do progress.

GenCerv is a more accurate Cervical Cancer Screening tool:
- Differentiates benign HPV infections from precancerous lesions
- Higher specificity and positive predictive value than HPV DNA testing
- Lower false positives than current cervical cancer screening standards

The HPV Specificity Spectrum
Screen provides improved specificity of cancer detection.

Using cutting-edge technology, GenCerv is able to detect and quantify the expression of HPV E6 and E7, acutely predict cervical cancer progression.

HPVCerviCa

5% of HPV-positive patients have cervical cancer in their future. Our test identifies them in just 24 hours.

Using a patient-sourced Pap test sample, the HPVCerviCa™ test detects cervical cancer and pre-cancer by identifying the oncogenic activity of HPV in infected cervical cells. Unlike a standard Pap test with a result to HPV, HPVCerviCa™ gives patients and pre-cancer test results.

Benefits to Your Practice:
- No additional sample to take—HPVCerviCa™ uses the patient's existing Pap sample
- Get clear, accurate results in just 24 hours
- Increase the accuracy of cervical cancer screenings from 70% to over 100%
- Significantly reduce false positives
- Eliminate unnecessary biopsies and colposcopies
- Detect cancer, not just risk, earlier than ever

Benefits to Your Patient:
- Reduces anxiety and stress caused by false positives
- Reduces the stress of waiting for test results
- Negative HPVCerviCa™ screening confirms peace of mind for abnormal Pap patients
- No additional procedure to schedule
- Eliminates expensive, invasive diagnostic procedures
- Gives the treatment benefits of early diagnosis

Serving over 1,000 Women's Healthcare providers daily, PathGroup is the largest provider of women's services in the United States. We're proud to be the industry leader in the ever-changing world of diagnostics.
FOR IMMEDIATE RELEASE

IncellDx Signs Deal with Kindstar Global to Offer Novel HPV Technology in China

MENLO PARK, CA June 11, 2013 - IncellDx, Inc. announced today that it has reached an agreement to offer its proprietary laboratory test for the detection of oncogenic HPV E6, E7 mRNA in China.

The agreement with Kindstar Global, the largest esoteric diagnostic testing business in China, greatly augments IncellDx’s business presence in Asia, the company said.

This test is based upon IncellDx’s advanced molecular diagnostic technology for quantifying specific biomarkers that have been associated with an increased risk of progression to cervical cancer, and will broaden Kindstar’s current offerings to physicians and hospitals managing diseases associated with women’s health. Kindstar will be the first reference laboratory in China to offer this test.

Measuring the potential oncogenic activity of the human papillomavirus (HPV) in infected cervical cells, this novel technology functions by detecting and quantifying the expression of viral oncogenes responsible for triggering progression to cervical cancer, resulting in a higher specificity that existing tests lack.

“Offering this cutting-edge molecular technology to Chinese physicians not only builds our women’s health platform, it enhances Kindstar’s leading position in the fastest growing market in the world,” Kindstar founder and CEO Shiang Huang said.

Bruce K. Patterson MD, founder and CEO of IncellDx, commented “The high level of specificity our technology produces has a significant, positive economic impact on healthcare delivery costs by potentially reducing the number of unnecessary colposcopies/biopsies. We are pleased that our partnership with Kindstar will provide better healthcare outcomes for women in China.”

About IncellDx, Inc.
IncellDx, Inc. is a molecular diagnostics company dedicated to the detection and monitoring of life threatening diseases such as cervical cancer, breast cancer, HIV/AIDS, hepatitis, and organ transplant rejection. For more information, please visit www.incelldx.com.

Contact: Eric Hass
IncellDx, Inc.
(T) +1.650.777.7630
IncellDx Signs Deal with CureHealth Diagnostics to Offer New HPV Technology in India

MENLO PARK - June 21, 2013, IncellDx announced today that it has reached an agreement to offer its proprietary laboratory test for the detection of oncogenic HPV E6, E7 mRNA in India.

The agreement with CureHealth Diagnostics of New Delhi increases IncellDx’s presence in the India subcontinent and Middle East, the company said.

This test is based upon IncellDx’s advanced molecular diagnostic technology for quantifying specific biomarkers and identifying cellular morphometric changes that have been associated with an increased risk of progression to cervical cancer, and will serve as a significant resource to physicians and hospitals managing diseases associated with women’s health. CureHealth will be the first reference laboratory in India to offer this test.

Measuring the potential oncogenic activity of the human papillomavirus (HPV) in infected cervical cells, this novel test functions by detecting and quantifying the expression of viral oncoproteins responsible for triggering progression, resulting in a higher specificity that existing tests lack. Specificity of a clinical test procedure determines the ability of a test procedure to detect no disease in a population of healthy, non-diseased people; meaning thereby no false positive results.

“IncellDx technology utilizes a flow-cytometry based method that can be used to identify the overexpression of HPV-encoded oncoproteins, offering a better indicator of persistent HPV infections than can be accomplished by identifying the presence of free, un-reactive or harmless DNA infection alone,” said Dr. Dinesh Gupta, PhD, Laboratory Director of CureHealth. “This addition to our growing line of molecular diagnostic tests for women’s health (cervical cancer, breast cancer and sexually transmittable diseases) underscores our expanding specialization in advanced clinical and diagnostic testing. We intend to use this test initially for patients who have been seen carrying primary lesions by standard techniques such as VIA/ VILI with or without Pap test or with unclear colposcopic findings.”

Bruce K. Patterson MD, founder and CEO of IncellDx, commented “The high level of specificity our technology produces has a significant, positive economic impact on healthcare delivery costs by rationalising the number of unnecessary colposcopy directed biopsies. We are excited that our partnership with CureHealth Diagnostics will expand our global reach as well as provide better healthcare outcomes for women in India and the subcontinent countries.”

About IncellDx, Inc.
IncellDx, Inc. is a molecular diagnostics company dedicated to the detection and monitoring of life threatening diseases such as cervical cancer, breast cancer, HIV/AIDS, hepatitis, and organ transplant rejection. For more information, please visit www.incelldx.com.

Contact: Eric Hass
IncellDx, Inc.
(T) +1.650.777.7630
July 2012, IncellDx was awarded the Frost & Sullivan Leadership Award in the Molecular Diagnostics Market. Frost & Sullivan cited IncellDx’s cervical cancer testing methodology, HPV OncoTest, as the company’s “greatest contribution” and the “gold standard for gynecological care.”

OncoTest detects the presence of cell changes due to persistent HPV infection, enabling physicians to distinguish between benign infection and precancerous disease — thereby eliminating the many instances of “false positives” resulting from other test methods. As a result, a woman’s increased risk for future development of cervical cancer can be determined with remarkable accuracy and unnecessary invasive procedures can be avoided.

The HPV OncoTest technology measures the quantity of over expression of E6/E7 mRNA, the cancer causing genes of HPV, in each cell and the total proportion of cells that are over expressing E6/E7 mRNA. This information has the promise of providing more specific indication that an HPV infection is transforming into cervical cancer. The HPV OncoTest can be performed directly from routine liquid based cytology samples and provides results in 3-5 hours.

May 2011, IncellDx launched OncoTest 3DX, the next generation of the HPV OncoTest. By providing both molecular and morphological data about a sample, OncoTest 3DX allows laboratories to completely digitize the cytopathology process.

June 2011, Enzo Biochem Inc. (New York, NY) announced that its Enzo Clinical Labs subsidiary had reached an agreement with IncellDx for the rights to market HPV OncoTest, a proprietary flow-cytometry based method that can be used to identify the genetic expression of HPV that has already integrated into the cell. This according to IncellDx offers a better indicator of serious HPV infections than can be accomplished by identifying the presence of the virus alone.
Contact Information

You are most welcome if YOU have a plan...

Dr Dinesh Gupta
General Director
Tel +91 98103 14638

Pradeep Sharma
General Manager
Tel +91 99710 99982

Company Information

234A, Chandi Plaza, Sant Nagar,
East of Kailash, New Delhi- 110065. India
Tel +91 11 2646 2636
Fax +91 11 4105 5709
www.genecell.in