HPV

Human Papillomavirus

HPV Type-Detect® 4.0 by Multiplex Real-Time PCR

Human Papillomavirus (HPV)

Papillomaviruses are a diverse group of viruses that have been found in more than 20 different mammalian species. In the 1980s, the newly developed techniques of molecular biology enabled the detection of many human papillomaviruses (HPVs) in benign and malignant lesions. To date, there are more than 100 HPV types. An HPV type is defined as a complete genome whose L1 gene sequence is at least 10% dissimilar to that of any other HPV type.

EPIDEMIOLOGY

- Over 40 HPV types infect the anogenital tract, 15 of them have been classified as high-risk for development of cervical cancer, 3 have been classified as probable high-risk, 12 have been classified as low-risk and 3 are considered as undetermined risk.
- HPV types associated with an increased risk of malignancy vary by geographic location. For example, HPV-16 is found in 77% of cervical cancers in Germany, 71% in South America, 59% in the United States, but only 33% to 39% in Japan.
- HPV infection shows a peak prevalence in women below age 25, a decrease among women aged 35 to 54, and a second peak after age 55.
- HPV infection in men: A recent Danish study has found 33.8% HPV prevalence (n=374 male conscripts 18 to 29 years) by PCR.
- HPV infection was detected in 70% of the male partners of HPV infected women.
- Of patients with penile lesions are found 99.5% to be HPV positive.
- In family: The most common HPV profile was high-risk (HR) HPV in all family members (29%), followed by HPV-positive mother-infant pairs (26%). HPV-positive father-infant pairs were less frequent (11%), and in 8% of the families, only the infant was HR HPV positive.
- In infants: HPV DNA was detected in 15% of the genital and 10% of the oral samples at birth, reaching peaks of 18% and 21%, respectively, at 6 months, and declining to 10% by 24 months.
- In adolescents: Cumulative HPV incident rates have been approximately 40% and prevalence rates as high as 80%.
- Despite the rate of anogenital infection, very few HPV infections result in cellular changes, genital warts, intraepithelial neoplasia, or cancer. Most infections (70% to 90%) are eliminated by the host immune system and become undetectable within 6 to 10 months.
- Infections with multiple HPV types are common and the average duration of infection with a specific HPV type is less than 6 months.

HPV IN ANOGENITAL CANCERS

- Cervical cancer is the second most common cancer among women world wide, with a mean age standardized incidence rate varying from 11.3 per 100,000 women in more developed countries to 18.7 per 100,000 women in less developed countries. The link between high-risk HPV and the development of cervical cancer is statistically greater than the link between smoking and lung cancer.
- The life-time risk of ever contracting HPV is estimated to be 80%. Despite the high prevalence of HPV in cervical cancer, very few HPV-infected individuals progress to invasive cervical cancer.
- HR-HPV has been detected in up to 99.7% of cervical squamous-cell carcinomas and 94% to 100% of cervical-adeno and the adenosquamous carcinomas.
- HPV type distribution in cervical cancer: Of the more than 40 HPV types found in the genital tract, HPV-16 accounts for some 50% to 60% of the cervical cancer cases in most countries, followed by HPV 18: 10% to 20%, HPV 45: 4% to 8%, and HPV 31: 1% to 5%. The five most common HR HPVs (16, 18, 45, 31 and 33) account for 80% of the distribution in squamous-cell cancers and of 94% of adenocarcinomas.

HYBRID CAPTURE® 2 HIGH-RISK HPV DNA TEST

- The specimen is denatured in the laboratory, and the liberated single-stranded DNA is hybridized in a solution with a RNA probe mix consisting of five low-risk genotypes (6, 11, 42, 43 and 44), and 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).
- The resulting bound DNA-RNA "hybrids" are reacted with an antibody directed against the hybrids.
- A chemiluminescent substrate, which binds to the antibody, is added and a signal output is recorded.
- Among women which are 30 to 35 years or older, the sensitivity of a single lifetime HC2 test for detection of high-grade dysplasia ranges from 80% to 90%, and has a specificity of 57% to 89%.
- The HC2 assay limitations:
  - » HC2 assay can not identify HPV individual types
  - » The detection of the HC2 assay is about 5,000 HPV genome equivalents which makes it less sensitive than PCR.
  - » Cross-reactivity of the two probe cocktails may reduce the clinical relevance of a positive result.
  - » Patients with cervical cancer may have poor recovery of HPV because of tumor necrosis and bleeding which may alter the test results.
  - » Unable to detect HR HPV Type 66.

HPV TYPE-DETECT® 4.0 by Multiplex Real-Time PCR

- MDL provides minimally-invasive, simple specimen collection methods for HPV testing using either cervico-vaginal swabs for females utilizing the ***OneSwab***® or ThinPrep® specimen collection platforms and urethral swab for males via the ***OneSwab***® specimen collection platform. The sample is collected from the endocervix and ectocervix with the which is then placed in the transport medium.
- HPV Type-Detect® 4.0 by Multiplex Real-Time PCR can detect and differentiate between 13 specific HPV types.
- Types Detected:
  High-risk, high prevalence: 16, 18
  High-risk: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

ADVANTAGES OF HPV TYPE-DETECT® 3.0

- Since 40% of HPV infections are coinfections, HPV Type-Detect® 4.0 by Multiplex Real-Time PCR can be used to differentiate between newly acquired HPV types and pre-existing infections when applied over time.
- Although the genetic variation among HPV types is merely 10%, HPV Type-Detect® 4.0 by Multiplex Real-Time PCR is highly specific without known cross-reaction to other HPV types.
- In HPV-vaccine recipients, HPV Type-Detect® 4.0 by Multiplex Real-Time PCR can be used to monitor successful immunization and patient stratification as well as to determine if patients have been infected with an HPV genotype other than that protected by the vaccine.

HPV VACCINE

- There are two different types of vaccines: prophylactic vaccines that would elicit an antibody response and prevent infection, and therapeutic vaccines that induce a specific and cell mediated response leading to regression of pre-existing lesions.
- In June 2006, the quadrivalent HPV vaccine for types 6,11,16,18 (Gardasil®, manufactured by Merck and Co., Inc., Whitehouse Station, New Jersey) was licensed for use among females aged 9 to 26 years and is the first vaccine developed to protect against most HPV type-related cervical cancer, cervical cancer precursors, vaginal and vulvar cancer precursors, and anogenital warts.
- Prophylactic HPV vaccines would be given to children before natural exposure and the onset of sexual activity.
- In the Merck Research Study, a subset group of women who were HPV-16 DNA positive and anti HPV-16 seronegative at the time of enrollment and received the vaccine were less likely to develop subsequent HPV-16 related CIN 2/CIN 3 than those who received placebo injections.
- In a Phase II clinical trial of 276 women who received the quadrivalent vaccine, the efficacy for prevention of persistent infection was 89.5% with HPV 6, 11, 16 or 18. In a Phase III clinical trial of 5,442 women aged 16 to 23 years, vaccine efficacy was 100% for prevention of any grade CIN related to HPV types 6, 11, 16 or 18.
- The prophylactic HPV vaccines are effective only against the HR HPV-16 infection which accounts for over 50% of HPV high-risk infections in the US.
- It was found the prophylactic HPV vaccines did not provide any protection against HPV-seropositive individuals.
- Therapeutic vaccines are in their infancy compared with prophylactic vaccines. A number of these vaccines have been studied in phase I/II clinical trials including in women with CIN, vulvar intraepithelial neoplasia (VIN) and advanced cervical cancer.
- Vaccination will not eliminate the need for cervical cancer screening in the United States because not all HPV types that cause cervical cancer are included. It is not a substitute for routine cervical cancer screening, and vaccinated females should have cervical cancer screening as recommended.