CiNtec® PLUS Immunocytochemistry – Effective Triage Tool for Cervical Cancer Screening

Cervical Cancer – Overview
Cervical cancer is the third most common cancer in women worldwide. According to the WHO, deaths attributed to cervical disease among women ages 15-44 ranks in the top three causes of cancer-related deaths in the majority of countries. The early detection of cancer and pre-cancerous disease is of utmost importance to successfully fight cervical cancer, which can be cured with nearly 100% if detected early. With the implementation of Pap cytology-based screening programs, the incidence rate of cervical cancer has decreased very successfully by about 70%. But nowadays the incidence leveled off. Pap cytology is not reducing the cervical cancer incidence further. The human papilloma virus (HPV) is widely known to be the cause of cervical cancer (>99%). HPV is an extremely common sexually transmitted infection with a higher prevalence in younger women (~25% of women under 30 years and ~10% of women over 30 years). Most HPV infections do not lead to cervical cancer, with the majority of women clearing the infection. Only ~5% of the women who are infected with HR-HPV actually develop clinically relevant dysplastic lesions or cancer. Persistent infections with 14 high risk genotype human papilloma-viruses (HR-HPVs) cause >99% cervical cancer and its precursor lesions. Among those 14 genotypes worldwide, HPV-16 and 18 contribute to over 70% of all cervical cancer cases.

Current cervical screening methods include primary screening with cytology and co-testing, which includes the use of cytology and HPV testing upon initial screening. Also, based on multiple studies demonstrating the sensitivity of HPV screening to be superior to cytology, the use of primary HPV screening as an effective method to measure and address women’s risk and treatment for cervical cancer is discussed or has been already implemented recently in several countries. Conventional screening for cervical cancer has been successful, but the technologies have limitations: subjectivity and lack of acceptable sensitivity in Pap smears, and a lack of specificity in pooled HPV testing, particularly in younger women. There is a clear need for an objective triage test that combines high sensitivity and specificity, thereby continuing successful prevention of cancer, while also reducing unnecessary patient intervention.

CiNtec® PLUS Cytology – Concept and Medical Value
CiNtec® PLUS is an immunocytochemistry test to be used on cervical cytology samples (conventional smears or liquid based cytology (ThinPrep™/SurePath™, BD SurePath™) to detect two biomarkers, p16 and Ki-67. p16 is a cellular protein involved in cell cycle control; its over-expression is linked to the oncogenic transformation caused by persistent HR-HPV infections. Ki-67 is a cellular marker strictly associated with cell proliferation that can be detected in the nuclei of proliferating cells. Applied in combination, the co-detection of p16 and Ki-67 in the same cell is mutually exclusive of each other in cells with intact cell cycle and serves as an indicator of cell cycle de-regulation caused by HR-HPV induced oncogenic transformation and provides objective criteria to identify those women who are most likely to harbour high-grade disease and should be referred to colposcopy.

The addition of HPV DNA testing to cervical cancer screening has resulted in many advantages including the ability to increase screening intervals. Despite advantages, there are limitations to pooled HPV testing, such as the lack of effectiveness in LSIL triage, creation of the discordant (cytology negative/HPV positive) category in co-testing, and the inability to use HPV testing in women <30 years due to the high prevalence of transient HPV infections and the low specificity rate in this age population.

The CiNtec® PLUS Cytology biomarker dual-stain test has clinically demonstrated to be an efficient triage tool with a statistically significant increase in sensitivity over Pap cytology and a statistically significant improved specificity over HPV testing. When used as a triage test for Pap cytology, CiNtec® PLUS can reduce the number of women that require referral to colposcopy compared with HPV testing in the ASC-US population. In the LSIL population, where the only current management option is colposcopy, CiNtec® PLUS can detect those women where no colposcopic referral is needed. When used as a triage for HPV testing, CiNtec® PLUS has demonstrated high sensitivity and specificity in detecting ≥CIN2 lesions, thus avoiding unnecessary colposcopy and overtreatment. Also, in patients aged 30 and over, with a normal Pap cytology result, but positive for HPV, CiNtec® PLUS can add benefit through the detection of underlying ≥CIN2.