

## Healthcare industry BW

# Diagnosics for the early detection of cervical cancer

**The Pap test is regarded as the most successful test for cancer ever, and has saved the lives of many women. However, the test is associated with several weaknesses. The Heidelberg-based in vitro diagnostics company mtm laboratories AG develops and commercialises highly sensitive and highly specific immunochemical tests that provide greater reliability. These tests have the potential to revolutionise the early detection of cervical cancer.**



Cells of a Pap smear ("second-degree Pap": normal cell alterations)  
© Papanicolaou & Traut, 1943

Every year, 6,500 women are diagnosed with cervical cancer in Germany and 1,800 die from the disease. The number of deaths would be even higher were it not for cancer screening programmes that entitle all women over 20 in Germany to undergo annual testing for the presence of abnormal cervical cells. The mortality resulting from cervical cancer has decreased dramatically in countries offering regular cervical cancer screening programmes. Such a programme has been available in Germany since 1993. Regular screening tests help to detect premalignant (precancerous) and malignant (cancerous) processes in the cervix as early as possible and put treatment in place immediately. Therefore, the screening procedures enable the early diagnosis of cancer rather than prevention of disease, a differentiation that is important for oncologists. From the patients' perspective, it is the result that matters most, i.e. the ability to prevent the fatal outcome of cervical cancer.

## The Pap test

The Pap test (also known as Papanicolaou test or smear test) was developed by the Greek doctor G. N. Papanicolaou and is still one of the most important tools to identify the very early stages of disease in women. Cells are gathered from the outer opening of the cervix of the uterus and the endocervix, fixed, dyed and visually inspected under the microscope by pathologists for abnormalities. The introduction of the test was the beginning of cytodiagnosics being an important



Georgios Nikólaos Papanicolaou  
© Greek stamp

screening tool and contributing to the recognition of a strategy of preventive oncology that focuses on the prevention and early detection of cancerous diseases. The Pap test is nowadays regarded as the most successful "cancer test" ever. Millions of women have received the Pap test and deaths from cervical cancer have been greatly reduced because of the test (see below).

### **Papanicolaou and the beginning of preventive oncology**

Georgios Nikólaos (or George Nicolas as he was called when he emigrated to America) Papanicolaou was born in Kyme (Kími) on the Greek island of Euböa on 13th May 1883. At the age of 21, he received his medical degree from the University of Athens. He then decided to move to Germany to study the natural sciences. He joined Ernst Haeckel and August Weismann and earned his PhD in Munich. He also got married to Andromache Mavroyani, his life-long companion and supporter. Known as "Mrs. Pap", Andromache Mavroyani made a considerable contribution to her husband's efforts in getting cytology accepted as a basis for the early detection of cancer.

The couple moved to France where Papanicolaou worked as physiologist, but they then returned to Greece where he served as soldier in the Balkan Wars of 1912/1913. The penniless couple emigrated to the United States where Dr. Papanicolaou obtained a position as assistant in the Department of Anatomy of Cornell University, Ithaca, NY in 1913. He continued to work at Cornell for 47 years - until a few months before his death.

Although he laid the cytological foundations of his test in the 1920s and 1930s, it took quite a while before Papanicolaou's work was accepted. The significance of his findings was finally recognised in 1943, when Papanicolaou and Dr. Herbert Traut, a gynaecologist with whom he had worked for several years, published their findings in the famous monograph "Diagnosis of Uterine Cancer by the Vaginal Smear" (The Commonwealth Fund 1943, New York). The diagnostic procedure, which was subsequently named the Pap test, received growing attention in the 1950s when the USA, the Scandinavian countries and the Soviet Union used the Pap test to carry out systematic cervical cancer screening and early detection campaigns. Papanicolaou

received many awards and distinctions towards the end of his life, though he never received the Nobel Prize, despite having been suggested several times. George Nicolas Papanicolaou died on 18<sup>th</sup> February 1962 of heart failure, a short time prior to the opening of the Papanicolaou Research Institute in Miami, Florida. He is buried in Clinton, New Jersey.

## Uncertainties associated with the Pap test

Although the Pap test has saved the lives of millions of women, it nevertheless has its weaknesses. "False-negative" findings in which malignant alterations go undetected, and "false-positive" findings in which healthy cells or those that have changed their shape due to other influences are classified as precancerous cells are quite frequent. Repeated examinations can reduce the errors, but usually require a biopsy to substantiate the findings. Biopsies are quite invasive surgical inventions that are carried out every year on around 100,000 women in Germany alone.

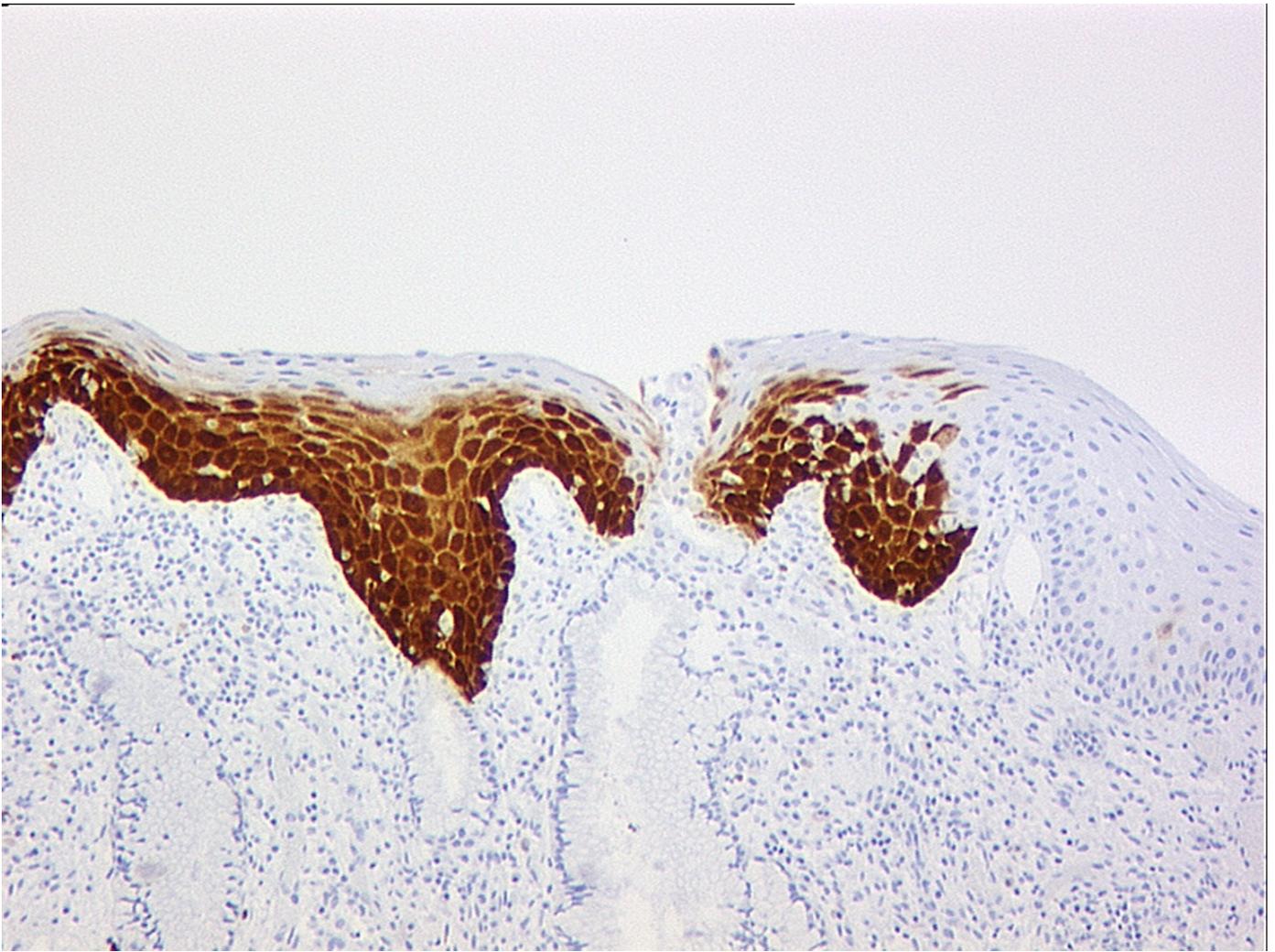
After Harald zur Hausen showed that human papillomaviruses (HPV) are the major cause of cervical carcinoma (see BioPro article of 15th March 2010: The first vaccination against cancer), the detection of papillomaviruses in the smear has been discussed as a potential means of detection of cervical cancer. The test focuses on the high-risk human papillomavirus types (HR-HPV), in particular on HPV16 and HPV18 which cause most of the HPV-associated cancer cases. However, this test is of no predictive value in healthy women because, although HPV infection is the cause of nearly all cases of cervical cancer, most infections with these virus types do not cause disease. Fortunately, cancer develops only rarely and it is common that the pathogens disappear naturally.

## Biomarker tests to improve the early detection of cervical cancer

The test methods developed by mtm laboratories enable a far more accurate diagnosis of precancerous lesions. The patent-protected test kits are based on the company's proprietary E6H4<sup>TM</sup> antibody clone. This was specifically developed for immunochemistry applications involving formalin-fixed, paraffin-embedded tissue sections and alcohol-fixed cell preparations. The assay measures the overexpression of the cyclin-dependent kinase inhibitor p16<sup>INK4a</sup>, a biomarker that is a direct indicator of the oncogenic activity of HR-HPV. The E6H4<sup>TM</sup> antibody, whose sensitivity and specificity has been confirmed and validated in more than 50 research studies, is combined in a kit with components manufactured according to GMP (good manufacturing practice) standards to ensure reproducible quality and results.

**mtm laboratories AG**, with its company headquarters in Heidelberg, develops, manufactures and commercialises in vitro diagnostics for the early detection and diagnosis of cervical carcinoma. The company, which was spun out of the German Cancer Research Center (DKFZ) in Heidelberg in 1999, is certified according to ISO 9001 and ISO 13485 standards. Subsidiaries in the USA, France, Italy and Spain and a large number of distributors enable mtm laboratories AG to serve the most important markets worldwide.

mtm laboratories AG is also developing biomarker-based diagnostics for other types of cancers. It cooperates with a comprehensive and continuously growing number of clinical research institutions, scientific research organisations and medical experts in the field of oncology and molecular pathology. As a result of these partnerships, mtm laboratories has established a quick and comprehensive method for the successful determination and clinical validation of biomarkers associated with the development of cancers.



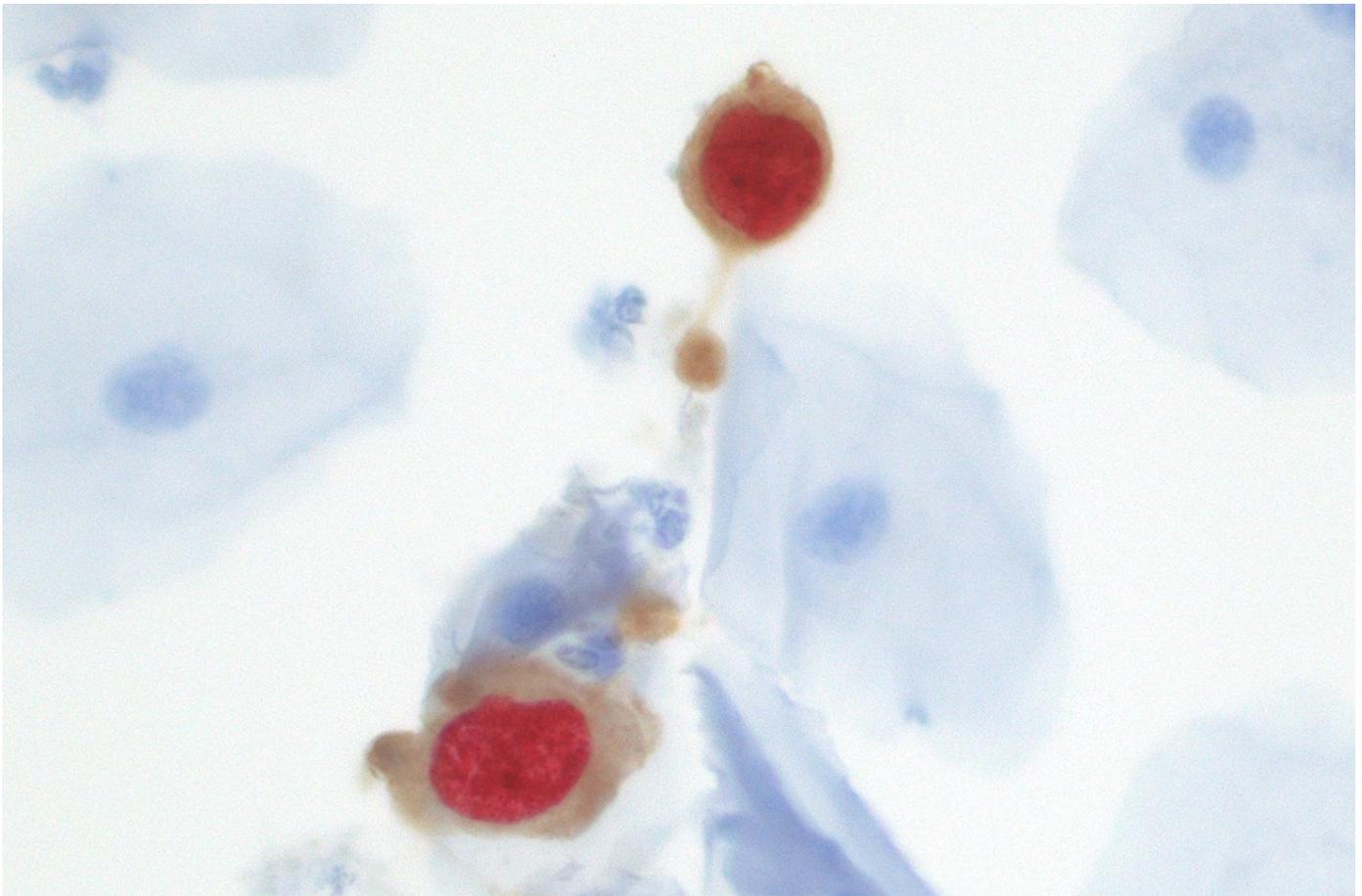
CINtec Histology staining of a biopsy slice.  
© mtm

The company's CINtec® Histology Kit is an immunohistochemistry assay for the qualitative detection of the p16<sup>INK4a</sup> antigen on slides prepared from formalin-fixed, paraffin-embedded cervical biopsies. The CINtec® Cytology Kit is used for use of smears and liquid-based cytology preparations. CINtec®PLUS is the company's most advanced screening kit for cervical cancer. It combines the p16 cell cycle regulator with Ki-67, a marker of active cell proliferation. The test combines high sensitivity and high specificity to detecting high-grade disease. As a recent large study has shown, CINtec®PLUS is far superior to the Pap test and HR-HPV testing (Denton KJ et al., Am. J. Clin. Pathol. 134: 12-21, 2010).

The company's Cervatex™ ELISA is an innovative test for the quantitative determination of p16<sup>INK4a</sup>. The test is based on the detection of the p16 biomarker in the cell lysate, which can easily be produced from cervical smears through heating. The Cervatex® ELISA assay is independent from the morphological assessment of cell types and has the potential to revolutionise the early detection of cervical cancer. The assay has been available in Germany since early 2008.

**Further information:**

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CINtec®PLUS test: p16- and Ki-67 staining of cervical cells  
© mtm

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## Article

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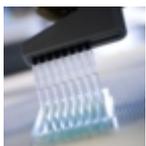
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## The article is part of the following dossiers



Disease prevention through better diagnostics

