

George Nicholas Papanicolaou (1883?1962) ^[1]

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George Nicholas Papanicolaou developed the Pap test in the United States during the twentieth century. The Pap test is a diagnostic procedure used to test for cervical cancer in women. Papanicolaou's work helped improve the reproductive health of women by providing an effective means of identifying precancerous cells and improving the likelihood of early treatment and survival of cervical cancer.

Papanicolaou was born 13 May 1883 in the city of Kymi on the island of Euboea in Greece. He was the third son of Maria Georgiou and Nikolas Papanicolaou. His father was a doctor and mayor of Kymi. In his youth, Papanicolaou studied literature, philosophy, foreign languages, and he played the violin. After high school in Athens, Greece, he studied medicine at the University of Athens in Athens. In 1904, at the age of twenty-one, he graduated from medical school with honors. In October of the same year, Papanicolaou was drafted into the army for military service and enrolled in the academy for reserve officers. Papanicolaou became assistant surgeon by the time he completed his military duty in August 1906. Rather than return to Kymi as a medical practitioner or in the military as a surgeon, Papanicolaou pursued a doctorate. At the Zoological Institute in Munich, Germany, he began studying the [differentiation](#) ^[2] and [determination](#) ^[3] in sex in *Daphnia* crustaceans, also called water fleas. He earned his PhD in Zoology from the University of Munich in 1910.

On 25 September 1910 he returned to Greece and married Andromache (Mary) Mavroyeni, the daughter of a high-ranking military officer. For their honeymoon, the Papanicolaous traveled Europe in 1911. They stopped to visit the Oceanographic Institute of Monaco in the city-state of Monaco. While at the Institute, Papanicolaou accepted an offer of a one-year position to join the staff. He studied the function of cells in marine organisms. While working at the Institute, Papanicolaou was the physician on an expedition on the oceanographic vessel *L'Hirondelle II*. Albert, prince of Monaco, headed the scientific expedition. In 1912, Papanicolaou and his wife returned to Greece due to his mother's death. That year, the Balkan War began and Papanicolaou stayed to serve as a reservist. As an army physician, he was promoted to second lieutenant in the medical corps. He kept that position until 1913.

While in the Greek army, Papanicolaou met volunteers from the US that informed him of the opportunities for scientific work in the US. Papanicolaou and his wife moved to the US in 1913 and took jobs at a department store in New York City, New York. Papanicolaou was hired as a technician in the department of pathology of the New York Hospital in New York City, where he studied cells under a [microscope](#) ^[4], looking for signs of disease. A year later, he became a research assistant in the department of anatomy at [Cornell University](#) ^[5] Medical College in New York City. He worked under the guidance of Charles Stockard, who directed the department of anatomy. Stockard researched the effects of alcohol on [germ cells](#) ^[6], embryos, and offspring. He studied the adverse effects of alcohol on the offspring of guinea pigs.

Because Papanicolaou worked with Stockard, he also used guinea pigs to conduct research

on the sexual cycle. In 1917, Papanicolaou began studying the vaginal discharge of guinea pigs. Papanicolaou attempted to pinpoint the time of [ovulation](#) [7], when the ovaries released fully developed eggs, in guinea pigs. He aimed to obtain [egg](#) [8] cells in their different stages of maturation. To do so, he collected cells from [guinea pig](#) [9] vaginas, smeared them on a glass plate, and observed them under a [microscope](#) [4]. Papanicolaou looked for traces of blood in guinea pigs during the sexual cycle as a means to identify the time of [ovulation](#) [7]. He performed daily examinations of vaginal fluid from guinea pigs but found no traces of menstrual blood, such as that found in other mammals like cows, [humans](#) [10], and other primates.

Instead, Papanicolaou observed that the epithelial cells of the [vagina](#) [11], collected along with the fluid, came in many forms. Epithelial cells cover outside layers of organs, which protect them against environmental contaminants and, in some cases, also lubricate through the secretion of mucus. Papanicolaou noted that the different forms of the cells went through a fifteen- to sixteen-day cycle, which he correlated with the changes in appearance of the [uterus](#) [12] and [ovary](#) [13] during the guinea pigs' sexual cycle. Papanicolaou's results led to a standard technique for studying sexual cycles in laboratory animals, including mice and rats. Stockard and Papanicolaou coauthored two papers on the research.

Papanicolaou then began researching whether or not variations in the vaginal cells of women correlated with their menstrual cycles. Papanicolaou used the same method of collecting vaginal fluid to women, which included collecting the sample, smearing it on a glass plate, and observing the cells under a [microscope](#) [4]. In 1923, he performed the first of what was later called the Pap test on his wife. Two years later, he began a larger study, taking samples from women who worked at the New York Women's Hospital in New York City. To gather samples, Papanicolaou inserted a metal instrument, called as a speculum, into the [vagina](#) [11]. The speculum kept the [vagina](#) [11] open so that the [cervix](#) [14] could be seen. Papanicolaou then scraped a sample of cells and mucus from the outside of the [cervix](#) [14] with a spatula, and also swabbed the inside of the [cervix](#) [14] with a cotton-tipped swab. He prepared the smears, or cell samples, for microscopic observation in a laboratory.

In some of the samples, Papanicolaou found abnormal-looking cells that he diagnosed as being cancerous. He began collecting samples from women with cervical cancer and confirmed that his technique could identify the presence of cervical cancer. He presented his technique as a new way to diagnose cancer at the Third Race Betterment Conference in Battle Creek, Michigan, in January 1928. Few doctors adopted his technique. At the time, the established convention to diagnose cervical cancer was to perform a biopsy to retrieve tissue samples from the [cervix](#) [14]. Papanicolaou stated that biopsies remained necessary for accurate diagnoses, and many other doctors said his technique was superfluous.

In 1939, Papanicolaou partnered with Herbert Traut. Traut worked in the gynecology and obstetrics department of [Cornell University](#) [5] and helped Papanicolaou set up a clinical trial through the New York Hospital. In the trial, all women seeking gynecologic services had a vaginal sample collected and analyzed by Papanicolaou. Papanicolaou identified many cases of otherwise undiagnosed cervical or uterine cancer. He caught some tumors so early that they were not visible to the naked eye and the women had no symptoms. Traut and Papanicolaou published their findings in 1941.

Prior to the Pap test, cervical cancer was often difficult to diagnose because it grew slowly and often showed no symptoms. Medical professionals agreed that identifying and treating

cervical cancer in its initial stages was the best way to treat it. However, before cervical cancers become malignant, they cause symptoms or discomfort. Without a prescreening diagnostic tool like the Pap test, researchers and health professionals usually could not detect cervical cancer until it reached an advanced stage. By the time physical symptoms manifested themselves, it was often too late for treatment. Papanicolaou spent the next ten years doing more studies to show the effectiveness and value of the Pap test. He also taught others how to perform the test and analyze the cells for signs of cancer. After Papanicolaou published an article in 1941 about using the Pap test to diagnose uterine cancer, physicians began using his techniques, and the Pap test became popular in the US. In 1954, he wrote a book detailing all of his methods and observations, called *Atlas of Exfoliative Cytology*.

In 1957, Papanicolaou and his wife returned to Europe. The royal family of Greece met with the Papanicolaous on Corfu, an island in Greece, and offered a previous royal residence as a site for a research institute named after Papanicolaou. However, without adequate funding for the idea, the Papanicolaous returned to the United States. In 1961, Papanicolaou became director of the Cancer Research Institute of Miami in Miami, Florida.

Papanicolaou received many accolades for his contributions to the detection of cervical cancer. Papanicolaou received the Lasker Award in 1950. In 1955, he was a recipient of the Bertner Award conferred to him by University of Texas in Houston, Texas, for cancer related research. Several countries have created postage stamps honoring him, and the 10,000 drachma note in Greece bears his face.

Three months after arriving in Miami, Papanicolaou died on 19 February 1962 from a heart attack. The research institute honored his life by renaming the institution, the Papanicolaou Cancer Research Institute in November of 1962.

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Subject

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