

# What Every Woman Should Know about Cervical Cancer

Nenad Markovic • Olivera Markovic

# What Every Woman Should Know about Cervical Cancer

Revised and Updated

Second Edition

 Springer

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## To Our Family

*In memory of our wonderful parents  
Dr. Trajko & Mila Saljinski and  
Prof. Svetomir K. & Olga Markovic,  
for raising us to search for truth, their  
magnificent devotion to the family  
and their love.*

*Our dear children Svetomir & Mila with love  
and hope they will continue our legacy.*

# Message from the Authors

Every woman should know that among 4000 women she will meet within 1 year, one will certainly have cervical cancer and that she might be this one woman, if she does not participate in regular cervical cancer screening.

During the lifespan while she is at risk (between 20 and 60 years of age), this chance is increasing to 1:10. Having the HPV disease, not the infection only, doubles the chance. At the same time, if detected on time, cervical cancer is completely a preventive disease – after removal of the suspect lesion, the woman is cured.

These statistical assumptions make the cervical cancer screening and removal of suspect lesions one of the most important additions to women's health and well-being.

But knowledge is power, and this power could and should be learned to be executed. Books are only tools that can help readers to improve themselves. The will is the essence of the conduct. The new edition is designed to move the will of women at risk for cervical cancer.

# Foreword to the 2016 Edition

In the Afterword of the 2008 Edition, the authors have emphasized the impact different strategies, new tools and subsequent guidelines – promoted by those who think it is their duty to recommend such guidelines – have made to the clinical practice developed to prevent the occurrence, to postpone the development, to facilitate therapy and palliation and to reduce suffering of subjects affected by cervical cancer.

The authors also have responded to the Call to Stop Cervical Cancer promoted by WHO (IARC) in 2008, whose one challenge, “To develop concerted action against cancer of the cervix,” is still a very actual one. In 2008, the stance of the authors was to “keep the tradition until the new option proves its superiority.”

Since, in between two editions, none of the proposed options proved its superiority to the standard Pap test (as measured by clinical outcomes), the authors have decided to introduce, in this new edition, their experience with MarkPap technology products, which in lieu of growing application of modern IT technology, telemedicine and mobile health seem to be the methodology of choice to move the ailing cervical cancer screening towards new horizons.

The following chapters/articles will present these new ideas:

- MarkPap Test – advantages and weaknesses
- Smart biomarker and digital imaging
- ITTHC and mobile opportunity
- Networking with medical image information
- Screen & Treat, WHO recommendation for one day resolution of cervical lesions, if present
- MEDYKO and one day Screen/Intervention Cycle

Proposal for a New Strategy for LMIC based upon US experience and MarkPap tools provided for specimen self-collection, specimen preparation, staining, reading, and interpretation, together with recommendation for on-site management of women with abnormal specimens.

## Between Two Editions

It has been 7 years since the book *What Every Woman Should Know About Cervical Cancer* has been published. The first edition was published as a compendium of information about cervical cancer necessary for women to know and to understand the disease in order to make educated decision and to be equipped with arguments to advocate about their health. The selected format was a monograph with personal experience being added to the medical information.

The expectation that this goal will be achieved was supported by the immense success of the cervical cancer screening campaign in the USA (1945–2005), where the negative trends of increase of cervical cancer prevalence and mortality were reversed into positive trends and both mortality and prevalence have been reduced by 80 % in 60 years of application. This success was undoubtedly related to the successful Pap test – the entire procedure including screening, diagnosis, and removal of lesions that can develop into cervical cancer.

Unfortunately, our book was not followed by proposals for change of health policy around the world and/or with offerings of new tools to enable the application of the new strategy. The cervical cancer market has been driven by the actual needs of local healthcare providers, who have been demanding tools for delivery of acute healthcare services. Cervical cancer prevention with cervical cancer screening, as it happened in the USA, needs large social actions like the cervical cancer campaign led by the American Cancer Society and supported by the US Congress. Without such support, the local healthcare providers are powerless, and women alone cannot help themselves.

This is why the current situation in the world is unacceptable for the twenty-first century.

In 2014, there were 7.33 billion people in the world, 2.5 billion women were at risk for cervical cancer, and only 20 % were protected by any type of cervical cancer screening (frequently substandard procedures); much more resources were spent on diagnosis and treatment for no results than it was invested in prevention for cure. Saving a woman's life is not only her problem, it is a problem for the entire society because women are not only tools for reproduction of population, but they are also competent, although not yet equivalent, partners for improving the society's life by

participating in economic and social growth. This aspect will be addressed in more details in the new edition.

The period between 2008 and 2014 has been characterized by fast-growing hopes that cervical cancer could be eradicated (due to HPV immunization and HPV testing) and also the fast balancing of this enthusiasm with the reality check that cancer is something more than a mere viral disease. Anyhow, during this period, HPV testing was improved with methods to assess separate (e.g., oncogenic) strains (16, 18), and testing for HPV was added to cytology screening, to VIA and to colposcopy.

Many competent institutions and professional societies in the USA, usually considered as authority for cervical cancer screening, have responded to this new situation and have changed, adjusted, or improved their guidelines for cervical cancer prevention, particularly, for screening for early lesions indicating possible cervical cancer growth.

Among them, the American Cancer Society (ACS, 2012), American Society for Cytopathology (ASC, 2014), American Society for Colposcopy and Cervical Pathology (ASCCP, 2010), American College for Obstetrics and Gynecology (ACOG, 2009), National Cancer Institute (NCI, 2014), US Preventive Services Task Force (USPSTF, 2012), Centers for Disease Control (CDC, 2012), Centers for Medicare Medicaid Services (CMS, 2014), and the World Health Organization (WHO Guidelines, 2013) have revisited their prior recommendations and came with new guidelines. They are presented in the new edition.

We have reviewed the prior and the updated new guidelines, and we found the following major changes that might have impact on cervical cancer screening practices and, probably, to the prognosis of future cervical cancer in the USA and, maybe, the world.

- Classic Pap smear remains as the basic reference and control test.
- Liquid-based Pap tests (ThinPrep, SurePath) have not produced convincing advantage versus the Pap smear to favor its replacement.
- Testing for HPV is to be reduced to only those strains which are connected to cervical cancer (16, 18).
- It is largely recommended that the period between testing is expanded from annual to between 1 and 3 years – many specific recommendations are given to selected age groups. We prefer annual screening and more sensitive but less harmful tests (perhaps, biomarker-based pathocytological assays).
- Clinical trials should rely more to the robust endpoints than to the surrogate endpoints as currently it will improve the value of the results and their inference.
- We have not found more attention given to modern IT, nor to the improvement of Papanicolaou staining with or without new biomarkers. This lack of attention needs to be addressed, because, as we think, both biomarkers and IT are the core of future cervical cancer screening and preventive medicine applied for cervical and cancer at large.

The most important myth generated after the success of Pap test was declared, and also the major target for those who would like to replace it or to join it partially, is the exacerbation of the cost of Pap test. The myth that Pap test is expensive must be analyzed and then rejected. Below is the first attempt in this direction.

The myth that Pap test is expensive is not true. The test itself – smear preparation, staining, and interpretation – is simple; it may take 1–2 h and the result is ready for reporting. However, the cost is increased because of the following:

- Specimen collection – medical doctor who must examine the subject and perform the pelvic exam
- Expert cytotechnologist and/or pathologist on site to read cytology information and to classify and report the findings
- Colposcopist (gynecologist) on site to validate (confirm) diagnosis
- Needs a medical doctor on site to receive the results and to decide about further procedure and management of women with abnormal specimens

All of this cost is eliminated by using MEDYKO™ (see below in Chap. 6).

These topics are addressed elsewhere in our new edition.

Once we completed these conclusions, the question arises on how to present the actual guidelines. Obviously links or only summaries with references will not have the impact as full guidelines. We decided to present them as originally published by their authors and to get permission for including them here by the publisher. Anyhow, in our new edition, we reserve a full chapter for presentation of the cervical cancer screening guidelines in effect after 2008 until 2015 (Chap. 4).

## **Tribute to the Readers and the Followers of Our Work**

The book *What Every Woman Should Know About Cervical Cancer* is our major publication, but it is not the only one. We were very active in communicating our ideas and achievements via publications, e-mail, or websites ([www.bioscicon.com](http://www.bioscicon.com) and [www.markpap.com](http://www.markpap.com)) and participating at various scientific and business meetings; promoting ideas in brochures, general public articles in proceedings and daily papers, as well as communicating directly with those who have expressed interest in our ideas, the strategy, and the tools meant to facilitate the application of the strategy.

In the period between 2008 and 2015, we have been very active communicating with scientists, professionals, students, and business and lay people all around the world. In response to many requests, we decided to expand this book with new chapters presenting the true information about different technologies – now in practice for cervical cancer screening – and to give women other options to educate themselves for a better decision on which way to go and what technology to ask for themselves and their families and friends.

Since a book is usually the most comprehensive compendium of answers to all questions, we have added the following new chapters: Chap. 4 “Cervical Cancer

Screening After 2008,” Chap. 5 “Global Cervical Cancer Screening,” Chap. 6 “New Strategy and Its Global Application,” Chap. 7 “New Tools,” Sect. 7.1 “MarkPap® Illustrated,” Sect. 7.2 “Information Technology Telehealth Center (ITTHC),” Sect. 7.3 “The New Integrative Complex MEDYKO,” Sect. 7.4 “Template for Telectytopathology,” “[Compendium of Guidelines Published Between 2008 and 2014](#),” “[Annex with Published Brochures, PPP](#),” and “Media with Video Presentations of the Topics in This Book.”

Between the two editions, one important fact has gained more appreciation: the value of outreach. The success of Pap test in America was achieved only when the percentage of screening participants had increased to more than 50 % of women at risk. At this crucial point, the ever-increasing trends of cervical cancer prevalence and mortality in the USA have reversed, and the trend continues to decrease while the outreach stays above 50 %. However, this success was achieved by healthcare providers, US Federal Government, health insurance, and health industry working in concert to provide public and professional education, to develop a national strategy, and to provide tools (infrastructure, equipment, personnel, and supply) to implement mass cervical cancer screening.

This understanding lacks in many developing countries which struggle with cervical cancer-induced problems, and their strategies are failing while the outreach stays low (at average below 20 %).

Fortunately, in case of cervical cancer screening, there are two robust measuring endpoints, the prevalence and mortality which cannot be influenced by many surrogate success/failure endpoints, and the true situation is easily obtainable. The general excuse that the mass cervical cancer is costly and unaffordable in many countries is also not true because of the current availability of modern IT and telemedicine tools and strategies.

Our new edition is dealing with this problem around the world (examples), and we hope, with this new text, to initiate reconsideration of the problem by the policy makers and to inspire them to adjust their policy to new conditions – which are now more favorable for women’s protection than ever before.

## About the Book and the Authors



During the 2006 Annual Meeting of the American Association for Cancer Research (AACR) in Washington, D.C., we had the pleasure to meet Dr. Cristina Alves dos Santos, Senior Publishing Editor, Cancer Research at Springer, NL. Discussing our work on cervical cancer screening which was presented at the meeting and how we came to our discovery, Dr. Dos Santos suggested that we consider submitting a manuscript to Springer for publishing.

In the beginning, we thought it would be interesting to write more about us, our work together as a husband-wife team, how we came to these discoveries, and how we proceeded with translational research and brought them from an idea to products.

However, this idea, no matter how attractive it seemed, had to be replaced with the actuality of the momentum – the necessity to provide women with a reference book to help them better navigate among new dilemmas and multiple options that modern medicine was offering.

What happened between the 2006 Annual Meeting of the AACR and our decision to write the book *What Every Woman Should Know About Cervical Cancer*? In 2006, the FDA approved the first HPV vaccine (Gardasil by Merck) and raised everybody's hopes for successful prevention of cervical cancer. It turned the accent from cytological screening to HPV testing and to molecular testing – a logical extension to include detecting viral particles. These molecular biology-related ideas called for a substantial increase of cervical cancer screening cost, and the funds-sensitive health insurance companies sounded alarm. The first signs of the worst solution appeared when Kaiser Permanente, accepting the new technology, recommended extending the periods between two cytological screenings for cervical cancer.

At that time, we were studying the relation between conventional Pap smear and the newly recommended liquid-based technologies in order to position our biomarker-based test to serve women's need best. One of the striking results from this study was the conclusion that the frequency of screening (annually) is probably better related to the success of Pap test (reduction of mortality from cervical cancer for 85 % in the USA) than the testing technology or false readings that have been a widely accepted argument against the Pap test. Recommending to extend the inter-screening periods was an alarming sign signaling to a danger that women could be again insufficiently protected against cervical cancer. More evidence-based information was needed to prevent an unwanted outcome.

We decided to use this opportunity and to write a book with emphasis on health education, a book that will synthesize the new achievements and will present them in the context of basic facts and prior advancements. Dr. dos Santos liked this idea, and when she accepted the proposed synopsis and contents of the book, we started to work. This is how the book *What Every Woman Should Know About Cervical Cancer* was born as a one-stop cervical cancer resource for women. Presenting medical concepts in plain terms with readily available advices, we thought we could help women:

1. To increase the awareness of risks and the availability of methods to prevent cervical cancer
2. To educate them of available cancer control measures: how to detect early curable precancerous disease and stop the cancer before it appears
3. To show them how to seek for appropriate help when cancer is diagnosed

This triad was intended to help women to promote their health, to ask educational questions from doctors, and to participate actively in their disease treatment, when needed.

Having experience with cancer patients and motivated by the current open forums, list-services, and chats on the Internet among women with precancer and cancer, we decided to devote more space in this book for discussions on the emotional, humane side of the problem of how to cope with the disease (Chap. 3). Since many women are interested in complementary medicine, we have chosen to include some carefully selected topics (e.g., relaxation and stress release, eating for optimal health, etc.). Dr. Olivera Markovic, having experience as a university health profes-

sor and being acquainted with the needs of health instructors and students, complemented the text to make the book useful for an academic environment. Dr. Nenad Markovic, an experienced oncologist, enriched the book with critical thinking on medical aspects of cervical cancer prevention (including HPV vaccination), control (past, current, and new screening methods), diagnosis (colposcopy, biopsy, histology), and therapy (surgical, radiotherapy, and chemotherapy), with emphasis on controversies and hopes created with the introduction of HPV vaccination. We hope these additions will be of benefit for medical personnel, students, and doctors.

The anticipated story about the authors had to be limited to their joint but abbreviated biography. Drs. Olivera and Nenad Markovic are peers, collaborators, and husband-wife lifetime partners. This was decided when they met in high school as best students in their generations and started and finished medical school on the same day in their hometown, Skopje, Macedonia, former Yugoslavia. They were supported by their wonderful parents. Mr. Svetomir Markovic, Nenad's father, was a renowned educator and professor of mathematics, and his mother Olga devoted her entire life to the family. Dr. Trajko Saljinski, Olivera's father, was DVM and Ph.D. in veterinary microbiology and senior scientific state counsel and director of the State Institute of Microbiology. He inspired her to love science since she was a little girl spending a lot of time with him in the laboratory. Her mother Mila, a talented vocal and instrumental artist and professor, ignited a love for music. Olivera was enrolled since age 6 in the school of music studying piano for 8 years.

After finishing their medical studies, Olivera and Nenad already married planned together their further education and specializations (residency and fellowships). Nenad decided for clinical medicine and specialized internal medicine, hematology, and oncology. Olivera decided for research and teaching and specialized medical biochemistry. At that time, they were immediately hired at the University Medical School in Skopje: Nenad at the University Clinic of Internal Medicine and Olivera at the Institute of Biochemistry, where they began their academic career as assistant professors. Nenad had his residency in internal medicine at the University of Skopje, at the University in Belgrade and later at the University of Lund, GH in Malmo, Sweden. There, working with Prof. Dr. Jan Waldenstrom, he discovered his affection for studying cellular structures and their functional meanings – a step that has influenced his further career. Olivera decided to postpone her specialization becoming a mother of their first child, Svetomir. She then completed the specialization in medical biochemistry at the University in Skopje and at the University in Belgrade. Soon after that, their second child, daughter Mila, was born.

At this time, Olivera was awarded the Fogarty International Research Fellowship at the National Institute of Health, Bethesda, Maryland. The family with two small children and a nanny arrived in Bethesda, Maryland. Olivera started her fellowship at the National Institute of Arthritis Metabolism and Digestive Diseases (NIAMDD) with Dr. N. Raphael Shulman as her mentor. Nenad soon was accepted as a clinical associate at the Leukemia Service, National Cancer Institute, to work with Dr. Edward Henderson.

Olivera started with her research on the maturation and differentiation of megakaryocytic-platelet blood lineage and discovered the importance of the change

of the megakaryocytic acid phosphatase isoenzyme spectrum along the lineage maturation. This work was later published in *Blood* together with Dr. Shulman and attracted a lot of scientific interest. Nenad implemented his experience from Malmo and was able to define several image analysis principles that are currently in use in digital image processing. It was an unforgettable time full of hard work, excitement, and scientific achievements. NIH became a second home to Drs. Markovic. At that time, they both started their doctoral dissertations.

After returning to Yugoslavia, they continued their graduate education working with Academic Professor Dr. Stanoje Stefanovic (Nenad) and Academic Professor Dr. Lubisa Rakic (Olivera). They both later defended their doctoral dissertations at the University in Belgrade. Nenad also completed the requirements for subspecialties in hematology and oncology. Olivera has already completed her specialization in medical biochemistry.

Soon, Nenad was awarded the NIH Fogarty International Research Fellowship at the National Cancer Institute, and the whole family moved again to Bethesda. Olivera's mentor, Dr. Shulman, offered her a position as visiting scientist to NIH. At NIH, Nenad and Olivera had the opportunity to work together on molecular imaging and quantitation of biologically active substances, primarily enzymes and their kinetics inside single cells. Together with their American colleagues, they pioneered in the application of image analysis in biomedicine. This was again a productive time full of hard work, discoveries, and publications, but also an amazing time working in the unique atmosphere at NIH meeting new colleagues and friends.

After the second stay at NIH, Olivera and Nenad again returned to the former Yugoslavia to transfer their knowledge and experience in their home country. Nenad continued with his practice, introduced the first leukemia protocols in Yugoslavia, and became head and later director of the University Clinic for Hematology at the University in Skopje.

Olivera developed a new clinical laboratory service at the University Children Hospital and became chief of Clinical Laboratories.

They continued their collaboration with NIH through scientific projects and joint programs involving young people. Nenad became the president of the Association of Yugoslavian Oncologists. At this position, he organized the National Congress with international participation and coordinated efforts of multiple specialists who were involved in providing healthcare in the field of oncology to create a unique policy that was accepted at the Congress. Later, this policy became a Resolution for Management of Malignant Diseases declared by the Federal Assembly of Yugoslavia.

In the follow-up to this Resolution, Drs. Markovic moved to Belgrade and Novi Sad where Nenad started to work on the implementation of this Resolution. With the full support of the Yugoslav Government, Nenad began developing a new cancer institute in Novi Sad, a copy of the NCI in Bethesda. This work was fully supported by the NCI and the US Government who prepared the feasibility study for this development. As a part of the same concept, Olivera developed a new drug and diagnostic test discovery and research laboratory in the University Clinical Center of the University of Belgrade. She was promoted head of the Laboratory for Research and Development at the University Clinical Center in Belgrade.

They both advanced as university professors and continued their joint research, published numerous publications, and participated as presenters, moderators, and organizers on national and international scientific meetings and congresses. To fulfill the Resolution's goals related to education, Nenad created the educational programs for undergraduate and graduate students which were adopted as the regular curriculum for medical studies in the School of Medicine, University of Novi Sad. Professor Dr. Nenad Markovic became the first chair of oncology in the whole of Yugoslavia. Unfortunately, this development was interrupted by the political disintegration of Yugoslavia (1990–1993), and Drs. Markovic returned to the USA where they had established their second residency and where their children were studying.

Between 1983 and 1993, Drs. Markovic were working on both continents being invited as visiting professors at Penn State University, the University of Pennsylvania, and Medical College of Pennsylvania (MCP). During that time, Dr. Nenad Markovic developed the first English medical school at the University in Novi Sad. The medical school was organized according to the curricula of MCP and the requirement of the ECFMG. The affiliation was built between the Belgrade and Novi Sad medical schools and MCP, with joint academic programs and exchange of students and faculties. The contribution provided by Dr. Walter Cohen, the president of MCP, Dean Dr. Alton Sutnick, and the chairman of the Department of Pharmacology Dr. Jay Roberts from the US side was crucial for the success of this affiliation. The school is still active, but the affiliation with MCP stopped by the same reason as the program for developing a national cancer center – political interests were stronger than the public needs for protection from cancer.

In the 1990s, the whole family moved to the USA and continued their scientific and academic careers. Their son, Svetomir, finished medical school and graduate school at MCP and his residency in internal medicine and hematology/oncology at the Mayo Clinic, Rochester, MN. He continues his brilliant career as a physician and researcher, partner, and associate professor at the Mayo Clinic. Their daughter Mila, a talented young lady, graduated from business school and became a business expert in the health insurance industry. She is living with her family in Toronto, Canada. Following the tradition of her mother and grandmothers, Mila is also a devoted parent to our grandson Michael. We are very proud of our children.

Olivera and Nenad continued working together and returned to Washington, D.C., metro area. Nenad joined the Food and Drug Administration, and Olivera continued teaching at universities and colleges in the Metro Area (University of Maryland at College Park, American University, Georgetown University). Besides basic medical science courses (biology, human anatomy and physiology, biochemistry, and pathophysiology), she also enjoyed teaching different health courses (women's health, personal and community health, drug use and abuse, and strategies in stress release). Dr. Olivera Markovic is still an active professor.

In the late 1990s, Drs. Markovic became troubled by the reports of Pap test diagnostic failures, law suits that followed, and laboratory liability and decided to respond to the call for improvement of Pap test technology issued by NIH, NCI Consensus Conference on Cervical Cancer in 1996. They recognized that in their

research, they have discovered something that might be helpful to ameliorate this situation, and they decided to explore this option for the benefit of American women in a short term and for the benefit of all women in the long-term planning. This is how they began working systematically on the cervical acid phosphatase (CAP). They found that this isoenzyme molecule is exclusively present in abnormal cervical precancerous and cancerous cells and that normal cervical epithelial cells are entirely negative on Pap specimens. They succeeded to visualize this biomarker of cellular abnormality as an intracellular red insoluble deposit on the bluish Papanicolaou-stained background. Making the abnormal cells more visible with the biomarker, they aimed to alleviate the disadvantage of Pap test related to the high percentage of false-negative results (because of missing abnormal cells). This is how cervical acid phosphatase-Papanicolaou test, the CAP-PAP test, was born and patented in the year 2000. In the meantime, Olivera decided to incorporate with BioSciCon, Inc., the R&D biotech and consulting company, to proceed with this research. Nenad joined later.

The NIH recognized the potentials of the new test and supported BioSciCon with SBIR Phase I and Phase II grants. Again, with the support of NIH, their alma mater, they conducted a translational research on 2000 patients from the general population and women at high risk and showed that the MarkPap<sup>®</sup> test (trademark for CAP-PAP test) is more accurate, faster, and less expensive. The test was given to a manufacturer to prepare a kit for in vitro diagnostic procedure, and the entire development is now awaiting the FDA approval for marketing in the USA. BioSciCon, Inc., appeared at the NIH success stories page ([http://grants1.nih.gov/grants/funding/sbir\\_successes/155.htm](http://grants1.nih.gov/grants/funding/sbir_successes/155.htm)).

The new biomarker also opens a new prospective for telemedicine, MarkPap<sup>®</sup> Digital (future Tele Pap test). Using an easy-to-use MarkPap Kit, specimens can be processed in a small laboratory or doctor's offices by a low-trained technician or a nurse. Since the abnormal cells are already marked red with the biomarker, the same person could see those cells in the microscope and immediately transmit their images to a laboratory with specialists for final evaluation. The result may be returned within hours. It means that the Pap test could be made available around the world bypassing the need for developing an expensive infrastructure. Drs. Markovic are currently working on the development of MarkPap<sup>®</sup> Digital.

There is one more important barrier for providing the Pap test globally and save women's lives. Women do not get screened not only because there is no Pap test accessible to them or they cannot afford it. They may have other restraints, like cultural/religious traditions preventing them to visit a gynecologist, or they are simply afraid of a pelvic exam and feel uncomfortable with it. In the USA, there are currently 20 million women who know about Pap test and have this test available, but do not take it. For all of them and the women around the world, our ultimate goal is to develop a self-sampling test, MarkPap<sup>®</sup> Self (future HomePap). It is the presence of the biomarker that opens this prospective, which has been impossible to accomplish until now. MarkPap<sup>®</sup> Digital and MarkPap<sup>®</sup> Self are expected to make the cervical cancer screening available to all women in the world. HPV vaccination

and biomarker-based cytological cervical cancer screening, like MarkPap test, open realistic hopes for the eradication of cervical cancer in the twenty-first century.

In order to accomplish this last task in their lifetime efforts, Dr. Olivera Markovic recently incorporated with a nonprofit organization, *Global Academy for Women's Health, Inc.* ([www.GAWH@markpap.com](http://www.GAWH@markpap.com)). The Academy's mission is the advancement in education and science for women's health. The book *What Every Women Should Know About Cervical Cancer* is the first accomplishment of the Global Academy for Women's Health, Inc.

Drs. Markovic currently reside in Rockville, Maryland, USA, and continue with their research. Until today, they authored more than 200 publications including books, chapters in books, invited lectures, scientific publications and presentations, and patents. Their current activity is devoted to the research and development of their proprietary MarkPap technology, writing and teaching, and hoping that thousands of women around the world will benefit from their hard work and devotion. This will be their legacy.

Drs. Markovic's biographies can be found in several bibliographical records, e.g., *Marquis Who's Who in America*, *Who's Who in the World*, *Who's Who in Science and Engineering*, *Who's Who is Healthcare*, *Who's Who of American Women*, and in *The International Bibliographical Centre, Cambridge, England*.

## The New Edition

The new edition covers the period between 2008 and 2015. This period was characterized with substantial changes in concept of cancer prevention, diagnosis, and treatment.

The mass cervical cancer screening for all 2.5 billion women at risk worldwide became the most wanted goal, and the new technology employing electronic devices promised that this goal could be achieved in the near future.

The basic changes and the new ideas are subject of this new edition. Indeed, it is a revised and updated edition, but because of these new issues, it had to be expanded.

The new book contains a prologue and an epilogue, 7 chapters, many sections, and articles. It is now enriched by original text of guidelines and images of new technologies and PowerPoint presentations on how they work. A few videos are added in the Annex to explain some important topics to large audiences.

Although designed as a monograph – a book presenting the personal opinion of their authors – this edition has plenty of information presented in their genuine form, which can be used as reference to the important topics discussed and challenged in the book.

## Readers Testimonials

I live on the south of Europe, in Belgrade, Serbia. I am not a medical doctor, but I am witnessing tragic, horrible stories about women suffering from cervical cancer, some of them very close to me. Serbia is a small country in Europe but, unfortunately, leading in mortality and morbidity from cervical cancer. Every year 1400 women get cervical cancer, and 500 lose the battle against this disease. I also found that the situation is the same in the wider region. Now, as the campaign for cervical cancer prevention started, I had a chance to obtain statistical data (not only from Serbia but for the whole region) that during the last 5 years, majority of women had not visited gynecologists' offices and have not had their Pap test done. In general, about two thirds of women do not have a regular gynecological exam. The purpose to investigate women's health situation in my country was the book *What Every Woman Should Know About Cervical Cancer* authored by Drs. Olivera and Nenad Markovic.

Questions started to pile up, e.g., why in the country, with an ancient culture having civilized kingdom in middle ages, whose churches and monasteries are under the UNESCO protection, which had hospitals in the twelfth century with instructions for a proper diet, and why the health education and health culture are on such low level. It is also a paradox that Serbia has excellent widely recognized medical doctors and scientists, but women ask for help when the time between the diagnosis and the end is so short. Dark and cruel Balkan history cannot be the only lasting alibi. In my opinion, the level of health culture is due to insufficient health education. A very thin connection exists between the elite and sophisticated science and the still conservative population, which are not open to each other for a variety of reasons.

Drs. Olivera and Nenad Markovic's book is a big discovery for me. It shows how to connect "difficult theories" of the science and "nontheoretical" mind of the general population. Two brilliant scientists, doctors, and professors have taught us a lesson that should be remembered. In the beginning, I scheduled doctor's appointments for myself and started to remind other women. The acceptance was beyond every expectation.

The unique feature of this book is the fact that it communicates equally successfully with health professionals and with those who are not, systematizing and broadening the professional material and, at the same time, giving to the general audience a proper “curable dose” of facts: carefully chosen and precisely defined subjects that expose problems and provide systematic and clear answers transfer the reader in the zone of sufficient understanding. This book “caught” me and kept me very interested to read everything until the last page. The discovery of a biomarker of cervical abnormality that I named B.M. “Olivera” is spreading in Belgrade because it has a universal value.

I think that what brings an extraordinary value to this book is putting the problem of cervical cancer on the existential level in its psychological and social aspects. With this, the authors have created a universal matrix which unites and organizes all elements for the fight against cervical cancer. I learned from this book, the way to transform endless paralytic energy of fear and despair (that every diagnosis of cancer is a deadly verdict) into a positive energy of fighting against the disease that creates hopes.

The problem is particularly delicate with cervical cancer which provokes multiple frustrations, guilt, and shame that leads to running away from the public scene to isolation and lowliness. The feeling of shame in a conservative environment is stronger than the feeling of fear. The essence of the book is demystification of cervical cancer, putting it together with other diseases which can be prevented, curing and cured IF detected on time.

With demystification of the disease, it comes to the public space where a patient has now a chance to talk about her problems and the disease and to share her worries with others. I have participated in this process so many times trying to give a hand and to help being a careful listener allowing the patient to tell me what she feels comfortable to tell. The attempt to cheer the patient, making her laugh, is sometimes successful, but sometimes it is not. However, real stories about real people with happy ending (particularly about women who the patient is acquainted with), a pleasant company that redirects the attention from the disease, a gentle hug, a small gift, a good book, or a flower would return maybe only for a moment a smile on a patient’s face. In all these situations, I have a feeling that this support has an additional value: Those who provide support to cervical cancer patients are emissaries of the core idea of Drs. Markovic’s book to bring encouragement and support. The book which these authors have given us is a real friend and companion.

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Prof. Dr. Smilja Tartalja

Sir Francis Bacon said, “Knowledge is power,” and when talking about cancer, knowledge brings a power that alleviates fear. After reading *What Every Woman Should Know About Cervical Cancer*, I came away from the book with a much better understanding of cervical cancer and with much less fear of it. As a lay person, who is also a veteran of breast cancer, I often find that it is difficult to read and understand medical books even when they are written for the general public. However, I found *What Every Woman Should Know About Cervical Cancer* to be highly readable. It approached the subject of cervical cancer not only from an individual woman’s perspective but also from a global perspective of woman’s health. It was very informative about why early detection is so vital and also presented ways to increase early detection of cervical cancer. The book arms women with valuable information in assessing cancer risk and common sense approaches to understanding our physiology. Of particular interest to me was the in-depth discussion of the widely available Pap test and its importance in screening for cancer, including the history of Pap testing from its discovery in the second half of the twentieth century to new technology such as MarkPap technology. Included in this segment is a frank discussion of the limitations of testing procedures including the troubling incidences of false-negative rates and ways to reduce those rates. The book also gives recommendations for women on how to discuss Pap test results with their doctors, something that every woman can benefit from. The book does not stop with just the physical side of health, however. In the final section of the book, there is a wonderful discussion of the mind-body connection and how important a positive, healthy mind-body connection is in promoting healing. I found the chapter on the stages of stress to be very illuminating and relevant not only for cancer patients but for everyone. This is a book I plan to recommend to my friends and relatives. I think it is a book that everyone would benefit from reading.

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## Afterword to 2008 Edition

The manuscript for the book *What Every Woman Should Know About Cervical Cancer* was submitted for publishing on September 30, 2007. The next month, the *2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests* were published in the October issue of the *Journal of Lower Genital Tract Disease* and in the October 2007 issue of the *American Journal of Obstetrics and Gynecology*.

The major difference between these 2006 Guidelines and the previous 2001 Guidelines, recommended by the same consensus conferences, is (1) the introduction of HPV DNA testing in the primary screening for cervical cancer and (2) adjustments made in the management of women with HPV DNA +/- tests. The adjustments were necessary to limit the fast-mounting cost of cervical cancer screening caused by the HPV testing. It is important to note that the authors of this clinical practice guidance document in the preamble stated clearly “these guidelines should never substitute for clinical judgment” giving back the power of decision to doctors and ultimately to patients themselves. This statement is a great support to our book and to our objective to help women understand the value of testing and medical options and to become educated patients who could contribute to the right diagnosis and treatment of their own conditions.

In the follow-up, along with the promotion of HPV testing, many limitations were noted, and the regulatory agencies (FDA, CDC), professional societies (CAP, ASC, ASCP), and even manufacturers of HPV vaccines and HPV tests indicated that the annual cytological testing should be considered as the gold standard not as an unnecessary alternative to the more complicated new testing. The American Cancer Society (ACS) acknowledged the HPV testing, but did not change their 2003 *ACS Guidelines for Early Detection of Cancer*, where Pap test (cytological screening) is the pivotal laboratory instrument to measure women’s risk for cervical cancer.

The introduction of HPV DNA testing into the primary screening has brought one big accomplishment; the Pap test is again recognized as the best test for cervical cancer control worldwide. Together with HPV vaccination (cancer prevention), the Pap test is becoming our hope for eradication of cervical cancer in the twenty-first

century. This change of perception has set aside the work of WHO, IARC Cervical Cancer Screening Group, PAHO, PATH, JHPIEGO, and other members of the Alliance for Cervical Cancer Prevention who considered Pap test as an unaffordable luxury for cervical cancer screening in low-resource countries and recommended alternative methods such as visual inspection with acetic acid (VIA), DNA HPV testing alone, and/or one-visit screen-and-treat approaches. Now, Pap test (cytological cervical cancer screening) is again the first priority, but the new question is what type of primary screening to be used. All of these options are addressed in our book.

Another major event, already discussed in this book, was the introduction of HPV vaccines (Merck's Gardasil and GlaxoSmithKline's Cervarix). This accomplishment has risen hopes that cervical cancer could be prevented by global vaccination (eliminate the HPV viral strains that can cause cervical cancer by eliminating them from the population), and a lot of money and effort was given to recruit people worldwide to accelerate the access of vaccines to the developing world.

The difference, between the day the manuscript for this book was submitted and the day it is published, was made by an enormous effort given to support those universal noble hopes. Supported by Melinda and Bill Gates Foundation, PATH has launched worldwide marketing to raise awareness of the preventability of cervical cancer deaths among all women in the world (1.7 billion at risk). A *Call to Stop Cervical Cancer*, which has been a logo for this campaign, is now beginning to institutionalize these activities into marketing entities coordinated by PATH. More information is available at <http://www.cervicalcanceraction.org>.

We have joined the campaign *Call to Stop Cervical Cancer* with a wish to contribute to this noble cause providing women with evidence-based information, which could educate them for making better decision about their own protection from cervical cancer.

Namely, stopping cervical cancer with vaccination, today, is only a wish until more effective vaccines are developed. Current vaccines cover only four HPV strains (out of at least 100) and are intended only for sexually naïve girls. Once infected with HPV, a woman remains infected for life with a weak natural immunity that clears the clinical signs until reinfection or reduction of immunity occurs. The current vaccine cannot add to or change this immunity. New vaccines are necessary. We hope that in the twenty-first century, these technical barriers will be overcome and there will be vaccines for all types of HPV and vaccines or other immunotherapies for noninfected and infected women alike; but, this time has not come yet, and a caution is needed to prevent general public disappointment (with all negative repercussions) when vaccinated women will start getting cervical cancers. To prevent this disappointment, all agencies involved in cervical cancer prevention and control insist on keeping cervical cancer screening programs alive for the next 10, 20, and more years

On the 4th of February, World Cancer Day, the International Agency for Research on Cancer (IARC) has published the *2007 Annual World Cancer Data Update* and *2008 Cancer Challenges*. The first, among General Challenges, is "To prevent those cancers that can be prevented." Two specific priorities are also related with cervical

cancer, “To implement what is known to reduce risk” and “To develop concerted action against cancer of the cervix.”

The call for “concerted action” was long due. Today, we have available tools for successful cervical cancer control (cytological screening in different versions), and tools for cervical cancer prevention are in the beginning of promising development (HPV vaccination), but we lack a substantial progress in cervical cancer therapy – surgical removal of early lesions that could develop into cancer is still the only therapy providing cure. This is why IARC is highlighting cervical cancer prevention and control.

The *Call to Stop Cervical Cancer* is also dedicated to prevention and control. The programs for development of new vaccines and programs to increase the awareness of vaccine protection are under way and well organized. Cervical cancer control is entangled with some confusion because of different options. The major dilemma is which examining procedure and what type of laboratory technique to recommend for mass cervical cancer screening worldwide. The stance of this book is to keep the tradition until the new option proves its superiority. It means regular annual cervical cancer screening with a biomarker-based cytological test, similar to the conventional Pap test or liquid-based Pap with HPV testing in addition (if necessary).

We see our contribution in this direction with the development of Home Test and MarkPap® Digital, two options available only because of our biomarker previously discussed in this book. We also believe that the medical device industry and the healthcare providers will join our vision to do whatever is possible:

- To make the collection of material and primary screening more affordable and more comfortable for every woman via development of new devices (e.g., Home Test)
- To improve the accuracy of diagnosis by introducing telecytology digital screening procedures (based on biomarker-based cytology, digital imaging, and online communication) between field sites where specimen is taken and processed and the remote screening sites where digital images of positive specimens are examined

In addition to the better and new HPV vaccines, we expect these two accomplishments, Home Test and Digital Screening, to become operational new tools for response to the unmet goals summarized in the *Call to Stop Cervical Cancer* in the twenty-first century.

# Acknowledgment

Our acknowledgments and gratitude go to the sponsors of this book: BioSciCon, Inc., Rockville, MD, USA, for both editions, and to Joseph E. and Marjorie B. Jones Foundation Washington, D.C., USA, for the first edition.

BioSciCon's mission is the improvement of women's health by saving women's lives and decreasing suffering from cervical cancer via developing new technologies for its prevention and control.

BioSciCon sponsored the formation of the Global Academy for Women's Health, Inc., a nonprofit organization dedicated to the advancement of education and science for promoting women's health around the world. This book is the first objective accomplished by the Global Academy for Women's Health, Inc. The Global Academy for Women's Health, Inc., is now the main sponsor of the second edition.

The Joseph E. and Marjorie B. Jones Foundation is a private, philanthropic institution dedicated to improving the quality of life for all people, particularly those residing in Washington, D.C., metro area, by funding medical research, supporting human services and healthcare initiatives, and furthering the cause of education. The Joseph E. and Marjorie B. Jones Foundation graciously provided a grant to the Global Academy for Women's Health, Inc.

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Professor Annie Dunn, Ph.D., partially edited the manuscript of the first edition, conducted the *Survey on Pap Test*, and contributed with a personal story. We also acknowledge Mr. Jim Grizzell for participating in the electronic *Survey*, Prof. Teresa Bevin for her support and contribution with a story, Dipl. Ing. Cvetko Saljinski for contributing with his artistic talent and knowledge of art photography, and Prof. Harriet Peck for participating in the editing of the manuscript of the first edition.

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After the first edition was published, motivated by the interest of both the general public and professionals, the authors continued with further R&D of MarkPap® technology, which particularly concentrated on developing countries. The reason was that, unfortunately, in spite of all investment and efforts and new approaches (like HPV detection and vaccination, automation), the situation did not improve significantly. The outreach for preventive measures against cervical cancer did not reach more than 10% in most of these countries. For example, in India, out of 300,000M women at risk, only 20M are being protected.

Realizing that more than price of a certain test and lack of infrastructure at the points-of-care (POC) are responsible for this failure, they concentrated their efforts to further develop infrastructure-independent methodologies.

The first success was the development of the MarkPap Telecytopathology Service for diagnosis at distance. The success was not only with conventional digital technologies (MarkPap® Digital), even more with the possibilities to use cell phone camera for transmission of cytological images (MarkPapMobile, Mobile Pap).

During this period of R&D (2008–2013), the authors acknowledge the support of the Johns Hopkins University, Montgomery County Campus, and its executive director Ms. Elaine Amir to the Global Academy for Women's Health, Inc.

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# Introduction 2016

*A woman should know that she could change her destiny, if she wishes and if she has the knowledge and tools to do so.*

This book is about educating women how to gain knowledge which will empower them to better control their own destiny and the destiny of their children and family at large.

I am a medical doctor practicing internal medicine, hematology, and oncology for more than 40 years, who has spent the recent 20 years in the field of cervical cancer because my wife, Dr. Olivera Markovic, has discovered that female cervical epithelium contains a bioactive protein (biomarker) which may lead and help them to conquer the fear from cervical cancer, and we together decided to devote our lives to bringing this biomarker to benefit all women.

During this period, I've seen thousands of women coming to my office for help because of their concerns, fears, and physical and psychological problems mostly related to cancer. Very early, I learned that the best way to deal with their problems is to hear the patient's complaints, to examine carefully, and to teach them to understand the cause of their concerns and to help them decide the best treatment approach available. I also found how much profound knowledge of the human soul Hippocrates of Kos had (ca. 480–375 BC) who wrote, "In practicing his profession, a doctor can rarely cure, could improve the condition many times, but always must help those who ask for help."

Dr. Olivera Markovic is a medical doctor and a Ph.D. in biochemistry, who was practicing laboratory medicine, but has devoted the last two decades of her professional career to cancer research. She is also a lifetime educator teaching basic medical science, science, and health-related courses. During the recent years, she has taught women's health and related courses at local colleges and universities in the greater Washington, D.C., metro area, where she learned how her students were unprepared for health challenges the adult life is bringing to them and learned how focused education could be both appreciative and successful.

When, because of the biomarker, we both dedicated our lives to women's health, we realized that the best way to accomplish new goals is to combine our research in bringing this biomarker to benefit all women with an appropriate education to help them understand better the beauty and the risks of being a woman in the modern world and the opportunities that all women have to protect themselves from cervical cancer. It is sad and unacceptable that millions of women, mothers, wives, sisters, daughters, and granddaughters, still die from a preventable disease in the twenty-first century.

In the period when we were in dilemma what to do first came the 2006 Experimental Biology Meeting in Washington, D.C., where we met the Springer representative Ms. Christine dos Santos who inspired us to write a book for Springer who will make it available to all women worldwide.

In the meantime, a major change in the strategy for prevention of cervical cancer occurred. Two pharmaceutical giants, Merck and GSK, developed vaccines to immunize women against oncogenic strains of HPV. This achievement has raised hopes for more effective protection from cervical cancer. However, since there is a long way to go to reach those hopes (decades), in the meantime, the newest strategy for cervical cancer prevention placed the emphasis on the motto *no women should be left without cytological screening protection*. Today, cytological screening for cervical cancer (Pap test) is not widely available. Only less than 10% of 1.7 billion women at risk have the opportunity to use this test in their developed and resourceful countries. The rest, most of them living in low-resource developing countries, does not have this opportunity. The World Health Organization and many governments all over the world are aware of the problems and are struggling to find ways to protect their female population with less expensive screening – but all efforts to replace the standard Pap test have not yet produced convincing results. The alternatives have not been shown to be at least not worse than the cytological testing.

Nevertheless, the news about vaccination has spread among women who are now increasingly asking whether, when, and how to immunize themselves and their daughters against cervical cancer. Because of the inaccessibility of the best cytological test, the cost of vaccination, uncertainty of long-term protection, ineffectiveness in all cancers, and many still unresolved questions but great hopes, the public is alerted, and women are upset which way to go and how. This is a perfect environment for a book like ours to bring a comprehensive insight to the problems as a basic knowledge and reference to websites where women will be able to follow the updated information.

Finally, because of the grave prognosis of cervical cancer, if not detected and treated on time, and the opportunity for cure if detected, and the early detection of cervical cancer or precancerosis, the Pap test became one of the most regulated medical diagnostic tests in the history. In addition to federal regulations (CLIA\*88 and amendments), many consensus conferences issued guidelines and guidance for medical procedures designed for early detection of cervical cancer and for products to be used in those procedures. All these documents are in public domain and are

available for review on the Internet. As much as this “openness” is important for public education, reading this literature without prior knowledge could be a source of unnecessary misunderstanding, frustration, and pain for readers. Our book will try to provide women with the basic knowledge, so they will read medical information with better understanding and, hopefully, will not regard the current medical strategies as biblical canons, but as temporary recommendations made by groups of experts based on their best knowledge and understanding. Emphasizing the transition of rules, we would like to open a window that neither bad diagnostic news are always bad as they look nor the good news should always be accepted as a total relief – a certain degree of uncertainty must always be present and second opinion asked. This makes the difference between educated and non-educated patient and could be of importance for women to better protect themselves in their lifelong struggle to avoid cervical cancer or to cure it if the first goal was not achieved.

In the period between the two editions of this book, the clinical trials have become an important medicolegal tool for proving the safety and efficacy of the new medical devices and became the important criterion to measure the compliance of the healthcare service delivery.

Most of those clinical trials were designed as FDA Clinical Trial Phase III in which the new method/device was tested upon a well-established and validated method versus a standard control method/device with intention to obtain objective data of the new device superiority, equivalence, or inferiority to the standard device. Standard statistical models were established and applied correctly.

The problem, however, rises with the control devices (used as standards).

While Pap test was clearly superior if measured with clinical outcomes (robust endpoints), many of the new devices have shown superiority in some or more laboratory and/or image parameters (surrogate endpoints) and, consequently, were approved for addition or even for alternative to Pap test.

This new policy has introduced more confusion than help, and comparison between screening or therapeutic methods and device supporting those methods became less clear.

This issue, with an attempt to clarify the truth, is discussed in the new edition.

As declared in the beginning, the new edition is the revised and upgraded first edition, which has been extended with several new issues; in particular, the emphasis was given to the New Strategy for Mass Cervical Cancer Screening Worldwide and to tools necessary to enable healthcare providers to implement this new strategy.

For the first time, this book treats the economic factors influencing mass cervical cancer screening and provides solutions on how to fund the crucial outreach of above 50 % of women at risk. This addition is important because it erases some of the myths that are holding wider application of screening methods in low- and middle-income countries; nonetheless, these countries have most needs for health assistance. In lieu of this view, our book could be considered as a contribution to the global efforts to reduce health discrepancies.