

To the Chairman of the Scientific Jury

According to Order R-525/21.01.2026

of the Vice Rector of the Research Institute,

MU Plovdiv

REVIEW

by Prof. Dr. Adelaide Ruseva,

Department of "Clinical Laboratory, Clinical Immunology and Allergology",
MU Pleven, regarding the dissertation

for the award of the educational and scientific degree "DOCTOR"

Author: Dr. Vesselina Stoyanova Koleva-Topova,

Doctoral Program "Clinical Laboratory"

Topic: "COMPARATIVE EVALUATION OF THE CLINICAL APPLICATION OF
BIOMARKERS AND ALGORITHMS IN ONCOGYNECOLOGY – SA 125, NE 4,
ROMA and CPH-I"

Scientific supervisors: Prof. Dr. Tanya Deneva, MD,

Assoc. Prof. Dr. Pavel Bochev, MD

Brief presentation of the doctoral student:

Dr. Koleva graduated from the First German Language High School with a gold medal for excellent results, studied medicine at MU-Sofia, majored in "Clinical Laboratory" in 2002, and in 2012 graduated from the Master's Degree in

Health Management at MU Sofia. She specialized in Göttingen and Stuttgart, Germany. She has twice completed exchange programs at Tokushukai hospitals in Japan, and in 2024 – a program for the development of international cooperation in the field of healthcare and health policies in China. Her professional path includes:

- Resident physician at the Clinic for Metabolic Diseases, University Hospital "Tsariza Ioanna" Sofia
 - Research associate at the Clinical Laboratory at the National Oncology Center, Sofia
 - Resident physician at the Clinical Laboratory of Lozenets Hospital, Sofia
 - Head of the Clinical Laboratory of UMBAL Tokuda from 2006 to the present
- Under her leadership, 7 doctors are trained and have completed training to acquire the specialty "Clinical Laboratory".

She speaks German, English and Russian.

Her competencies make it possible to be a member of a number of professional and scientific organizations, such as: Member of the Board of Directors of the "Tokuda Center for Clinical Studies", Chairman of the Ethics Committee at UMBAL Tokuda, Member of the Board of the Bulgarian Society of Clinical Laboratory, Member of the Expert Council in the specialty of Clinical Laboratory at the Ministry of Health, Member of the Joint Oncology National Network, Technical expert at the Bulgarian Accreditation Service in the field of "Accreditation of Medical Laboratories - ISO 15189".

From 2019 to the present, Dr. Koleva is a part-time lecturer at the Faculty of Medicine of Sofia University "Kliment Ohridski".

Relevance of the dissertation project: Gynecological oncological diseases continue to be a leading cause of morbidity and mortality among women worldwide. In this context, laboratory biomarkers play a key role in early diagnosis, monitoring and personalized therapeutic approaches. That is why the topic of laboratory biomarkers in gynecological oncology is extremely

relevant and dynamically developing, combining clinical significance with rapid development of new technologies in the field of laboratory medicine.

Structure: The presented dissertation project contains 228 pages, which include 105 figures and 53 tables. Contains: Abbreviations used, Introduction - 2 pages, Literature review - 40 pages, followed by clearly presented existing unsolved problems and logically constructed working hypotheses. The following are: Aim and objectives, Material and methods - 16 pages, Results - 117 pages, Discussion and conclusions - 17 pages, Contributions, Publications, Bibliography. The literature review is based on the publications of 156 authors, the majority of which were published after 2020. The literature review presents data on the prevalence of ovarian and uterine carcinoma, as well as general data on tumor markers, in-depth, extensive, but without propaedeutic details. The emphasis is on the clinical application of CA 125, HE4, the Risk of Malignancy Index (RMI), multimarker models, and algorithms for risk stratification for the presence of ovarian carcinoma.

Aim and objectives: Based on the established working hypotheses, this study formulates the following ambitious aim: To compare the clinical application of the biomarkers CA125 and HE4 and the ROMA and CPH-I algorithms in patients with oncogynecological diseases. 5 tasks are clearly formulated, sufficient to fulfill the set aim.

The study design includes both retrospective identification and prospective assessment of time to recurrence, time to progression and overall survival.

Material and methods: The study included 1647 women, divided into 8 groups. The inclusion and exclusion criteria are clearly defined. As a professional with enviable knowledge and extensive practical experience, Dr. Koleva presents not only the principles of the laboratory analyses and calibrations performed, but also presents data from their verification.

The results of the dissertation are presented in a comprehensible and clear manner in five sections, respectively, of the five tasks set. The first of them is related to: Development of reference values for CA 125, HE4, ROMA and CPH-I, specific to the Bulgarian population. This task is a real challenge because it requires high scientific precision, representativeness and standardization, but is essential for accurate diagnosis and effective treatment. The study included 246 healthy women aged between 20 and 82 years, divided into two groups: premenopausal and postmenopausal. The statistical test for normal distribution of the results showed a lack of Gaussian distribution of the results for HE4, CA125, ROMA and CPH-I in the reference groups from the Bulgarian population, therefore the derived upper reference limit corresponds to the 95th percentile. The reference limits are differentiated by age groups, as well as by menopausal status. The relationship between age and the values of HE4, CA125, ROMA and CPH-I was studied, using the Spearman Rho rank correlation coefficient. Reference limits of HE4 in pregnant women were derived, and the study included 52 healthy pregnant women in the first and second trimester of pregnancy. The results of the following four tasks reflect the estimated diagnostic significance of the two tumor markers and the ROMA and CPH-I indices for the detection of ovarian carcinoma and their clinical applicability in patients with endometrial carcinoma, their prognostic significance in terms of overall survival, recurrence rate, time to progression.

In the **Discussion** chapter, the results obtained for each of the five tasks set in the dissertation work are analyzed in the context of the scientific data on the problem presented in the literature review.

Conclusions: Logically, given the large-scale goal set in the dissertation, but also possible only for a laboratory specialist with great capacity, 14 significant conclusions have been drawn from the results obtained.

3 Contributions of a unique scientific nature have been formulated, 6 Contributions of a confirmatory nature, which I accept and for which I congratulate the author of the dissertation.

Dr. Koleva dedicates her dissertation "to her unforgettable teacher in clinical laboratory – Prof. Dr. Todor Shipkov", a respected specialist who has contributed significantly to the development of laboratory medicine and medical education in Bulgaria. With this in-depth study and with everything achieved so far in her professional development, Dr. Koleva unequivocally convinces that she is a worthy successor to the work of the professor.

The abstract is presented on 60 pages, reflecting precisely the most important moments of the dissertation work, emphasizing the obtained results, which are summarized here in 30 tables and illustrated with 67 figures. The conclusions drawn, the contributions of this study and the recommendations made are included.

In connection with the dissertation work, 3 full-text scientific publications and 2 participations in scientific forums are presented.

Conclusion:

This dissertation does not simply compare biomarkers and algorithms, but evaluates which tool, combination or approach truly improves the diagnosis and prognosis of oncogynecological diseases. I believe that this is a remarkable, precisely executed dissertation, large in volume and number of logically drawn conclusions and contributions. I am convinced that its results can be a valuable target for all laboratory physicians, as well as for clinicians in the field of oncogynecology. This comparative study of biomarkers and algorithms has significant value, increasing their diagnostic and prognostic

accuracy; promoting personalized medicine; providing evidence for health policies and good practices.

Due to the above, I confidently give my positive assessment and propose to the esteemed members of the scientific jury to vote positively for the acquisition of the educational and scientific degree DOCTOR by Dr. Vesselina Koleva-Topova.

Заличено на основание
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Prof. Dr. Adelaida Ruseva