Review

by Assoc. Prof. Dr. Ekaterina Boyanova Softova-Zlatarova, PhD

Scientific Specialty "General and Clinical Pathology"; MC "CITY LAB" Ltd - Varna

Subject: regarding the competition for the academic position of "**Associate Professor**" in "General and Clinical Pathology", within the field of higher education 7. "Healthcare and Sports", professional field 7.1. "Medicine", in the scientific specialty "General and Clinical Pathology", announced in the State Gazette, issue 85/08.10.2024, for the needs of the Department of General and Clinical Pathology, Forensic Medicine, and Deontology at the Medical University of Varna and the Clinic of General and Clinical Pathology at UMHAT "St. Marina" EAD - Varna.

According to the report No. 102/3334/28.11.2024 from Assoc. Professor Deyan Dzhenkov, PhD, Head of the Department of General and Clinical Pathology, Forensic Medicine and Deontology, decision according to protocol No. 31/02.12.2024 of the Faculty of Medicine at MU-Varna, order No. P-100/929/04.12.2024 in connection with the announced competition, and order No. P- 109/437/05.12.2024 of prof. Albena Kerekovska, PhD, Deputy Rector "Educational Activity" of MU-Varna, I was elected as an external member of a Scientific Jury, and according to protocol No. 1/16.12.2024 from the first meeting of the Scientific Jury, I have been appointed to prepare a review on the procedure for filling the academic position of "associate professor" in the specialty "General and Clinical Pathology", with candidates according to the announced competition, Chief Assistant Professor Dr. Martina Georgieva Stoeva, PhD, and Chief Assistant Professor Dr. Nadezhda Todorova Stefanova, PhD. According to the regulations for the competition, the candidates have submitted a complete set of materials on paper and electronic media with all the necessary documents specified in the Regulations for the terms and conditions for acquiring scientific degrees and occupying academic positions at the MU-Varna.

Brief biographical data and career development of Dr. Martina Georgieva Stoeva, PhD

Dr. Martina Georgieva Stoeva was born on 22.02.1988 in the town of Blagoevgrad. After completing her secondary education in 2006, she was admitted as a student at the Medical University of Varna, where in 2012 she completed her higher education with a degree of Master of Science in Medicine /Diploma with reg. No. 001897 / 15.11.2012 series MUV 001461/, issued by the Medical University of Varna.

Dr. Stoeva's professional development began in 2013, when she was appointed as a resident in the Clinic of General and Clinical Pathology at the University Hospital "St. Marina" EAD - Varna. After successfully passing the state examination, Dr. Stoeva obtained a Certificate of Recognized Specialty in General and Clinical Pathology /reg.№ 021479/20.02.2018, series MUV 2018, № 3942/, as of 01 January 2018. For the period from 2017 to 2022, she is a physician-assistant at the Clinic of General and Clinical Pathology at the University Hospital "St. Marina" – Varna. She is also a member of the Department of General and Clinical Pathology at the Medical University of Varna. In parallel with her professional career, Dr. Stoeva is successfully developing in the

academic field, as for the period from 2015-2017 she is a honorary assistant at the Department of "General and Clinical Pathology, Forensic Medicine and Deontology" at MU-Varna, from 2017 - 2022 she is an "Assistant Professor" - specialty "Medicine" at the aforementioned Department. According to the Order of the Rector of MU-Varna No. P-109-175/15.04.2022, after a competition for the position of "Chief Assistant Professor", announced in State Gazette No. 14/18.02.2022, from 2022-2024 Dr. Stoeva was appointed as "Chief Assistant Professor" - specialty "Medicine" at the Department, where she continues to work at present.

According to the Order of the Rector No. P-109-39/01.02.2019 and the decision of the Faculty Council of the Faculty of Medicine No. 17/14.01.2019, Dr. Martina Stoeva was enrolled as a full-time PhD student in the PhD program "Pathology and Cytopathology", and according to the Order No. P-109-41/21.01.2022 she was dismissed with the right to defend. On March 11, 2022, Dr. Stoeva successfully defended a dissertation on "Immunohistochemical expression of the necroptosis marker RIPK3 in breast carcinoma" and obtained the PhD degree in the scientific specialty "General and Clinical Pathology" / Diploma № 506/20.05.2022/.

Dr. Stoeva is a member of the Bulgarian Medical Union, the Varna branch of the SBU, and the Bulgarian Society of Pathology. She speaks level B2 English and has very good computer literacy. She has participated in national and international scientific events as an author and co-author in the writing of 22 articles with a total volume of 164 pages and 5 reports with a total volume of 11 pages. Of those submitted, Dr. Stoeva is 1st author in 4 publications; 2nd in 6, 3rd in 5, and post 3rd in 3 publications. As a team member, Dr. Stoeva has participated in 5 research projects under the Science Fund of MU-Varna. In order to improve her professional qualification, in the years 2015-2022 Dr. Stoeva has attended the courses, seminars, etc. held during this period, with particular significance among them stand out the five participations in the "European School of Pathology", with lectures and practical sessions related to gynecological diseases, thyroid gland, male urinary system, mammary gland and brain tumors.

Evaluation of scientific metrics in relation to participation in a competition for the academic position of "associate professor". Scientific research activity.

The works submitted for participation in the competition, reflecting Dr. Stoeva's scientific research activity in the period 2015-2024, include:

1. **Dissertation thesis** for obtaining the PhD degree on the topic: 'Immunohistochemical expression of the necroptosis marker RIPK3 in breast carcinoma';

2. Habilitation thesis - **"Monograph" on "Pathomorphology of carcinoma of the prostate gland"**, published by the Library of MU-Varna;

3. **16 full-text publications** in foreign and Bulgarian scientific journals /5 of which are with IF/, included in the academic reference in: **indicator G.7** - publications and reports published in scientific journals, refereed and indexed in world-known databases with scientific information, which is represented by ten /10/ articles, numbered from №1 to № 10, evaluated at 120,02 points, and included in indicator **G.8** - Publications and reports published in non-refereed peer-reviewed journals or published in edited collective volumes, represented by six/6/full-text articles, numbered

No. 1- No. 6, and assessed at 104,29 points. The total number of points obtained from the indicators G.7 and G.8 of the 16 full-text publications in scientific collections and journals other than those for the award of the PhD. is 224,31 points, with a required minimum of 200 points, indicating that **criterion G** of the minimum scientific metric requirements for the position of **Associate Professor** has been met;

4. **One full-text publication** in scientific journals and collections beyond the minimum scientific-metric requirements for the position of Associate Professor, evaluated with six /6/ points.

The dissertation for the PhD on "Immunohistochemical expression of the necroptosis marker RIPK3 in breast carcinoma" was evaluated by the Scientific Jury, from which it follows that criterion **A1** /number of points 50/ of the minimum requirements for holding the post of **Associate Professor** under the LDSSRB is fulfilled;

Habilitation thesis / **Monograph, containing 189 pages**, is published by Medical University - Varna, ISBN 978-619-221-469-2. In the academic reference for publications, citations and scientific profiles issued by the MU-Varna Library, the monograph is presented in **indicator B3** and is evaluated at 100 points, which provide the required minimum / 100 points / to meet **criterion B**;

For participation in the competition, Dr. Stoeva has submitted 4 citations in foreign scientific journals, refereed and indexed in world-renowned databases of scientific information **/WoS/Scopus/**, which according to the indicator D10-12 provide a total of **60** points /all citations in D10 are x15; 4 x 15points= **60** with the required minimum of 50 points/- i.e. **criterion D** is met.

The research activity and contributions of the scientific works of Dr. Martina Stoeva are in the following main areas:

1.Prostate cancer- monograph and publications G8: №1 and №2;

2.Rarely diagnosed diseases G7: № 2, № 4 and № 5;

3.Experimental morphology G7: №1 and №3;

4.Pathology of adipose tissue G8: №3 and №6;.

5.Tumor and non-tumor diseases of the head and neck G7: No. 6, No. 7, No. 8, No. 9, No. 10 and G8: No. 4;

6. Molecular mechanisms of carcinogenesis G8: No. 5;

7. Infectious Diseases - a full-text publication beyond the minimum science-metric requirements for the position of AP "Associate Professor".

The review of Dr. Stoeva's scientific contributions undoubtedly highlights not only the inherent multifaceted and diverse range of her scientific and practical interests, but also the extraordinary range of knowledge and skills she possesses and uses in her daily diagnostic work. Thanks to the experience and competence acquired over the years, Dr Stoeva is able to cope with the difficulties that often arise, especially in the diagnosis of situations that stand out for their unexpectedness.

Contributions related to the main areas of the dissertation and the scientific works presented by Dr. Stoeva:

I. The contributions in Dr. Stoeva's dissertation can be presented as **a/ contributions of an original nature**, and **b/ contributions of a practical-applied nature.**

1. Contributions of orginal nature. 1. A complex clinical-morphological and IHC-analysis of the receptor status of RIPK3, a marker of necroptosis in patients with mammary carcinoma; 2. An analysis of IHC-marker expression was performed with a view to clarifying its role for prognosis and survival in patients with breast carcinoma;

2. Contributions of practical-applied nature. 1. For the first time in our country the prognostic and predictive value of RIPK3 in patients with mammary carcinoma was determined; 2. The expression of RIPK3 was analyzed in relation to the Ki67 marker and receptor status in breast cancer patients; 3. RIPK3 expression was analyzed in relation to clinicomorphological parameters to determine the risk of metastasis.

II. Contributions in the articles submitted outside the thesis. Prostate cancer. Monograph on "Pathomorphology of prostate carcinoma". The scientific work is written on 189 pages and is illustrated with 40 figures and 16 tables, the majority of the figures are author's photographs of histological findings, reflecting both the morphological diversity of PC and that of benign and borderline lesions in the prostate. The embryology, anatomy, and histology of the prostate gland/PG, etiology of carcinoma, classification of PG tumors, staging, Gleason score, and Grade Group determination are presented and described in detail in successive chapters of the monograph. Dr. Stoeva draws attention to the emerging challenges in the histological differentiation of benign from malignant lesions, especially in cases of the "presence" of histological variants of PC mimicking benign lesions, and vice versa - the presence of benign lesions mimicking PC - factors that greatly complicate the diagnostic process. Attention in the monograph is also paid to the role and application of modern imaging techniques in the diagnosis of PC, as well as to the various methods applied in the treatment of carcinoma. Valuable for practice is the conclusion made by Dr. Stoeva **that "the integration of imaging results with histopathological data is most essential for the overall evaluation of each case".**

The "final chord" of the monograph, which leaves a very good impression on the readers of the scientific work, is the presentation of the own study, showing the results of the magnetic resonance imaging of 100 patients, reported by the system /PIRADS- to determine the risk of the presence of clinically significant malignancy/, compared with different clinic-morphological characteristics of the tumors - histological type, stage, degree of differentiation, perineural invasion, cribriform structure, etc.

Contributions in the monograph are presented in sequential order from one to 9, and relate to:

1. A comprehensive view of the structure of the prostate and the malignancies that can develop in it; 2. The latest classifications of tumors of the urinary and male reproductive systems / WHO 2022 / for staging of Prostate Cancer / 8th revision of the AJCC / are presented with appropriate

commentary; 3. The fact that accurate reporting of tumor differentiation is a process with marked subjectivism and a point of contention even among leading urologists is noted; 4. The most common problems giving rise to diagnostic misleading are discussed; 5.The determination of Gleason score is of utmost importance in therapeutic decision making; 6. A contribution of this monographic work is the presentation of a detailed differential diagnosis between prostate adenocarcinoma, benign lesions and normal anatomical structures; 7. A number of nosology entities are described in detail, and for each a specific morphologic aspect of the carcinoma is indicated that may lead to diagnostic "chaos"; 8. Approaches to each lesion considered, based on routine light microscopy and IHC studies, are suggested that would aid in diagnosis; 9. The monograph's contribution is the use of its own photographic material in the description of histological changes and their "mimics".

In conclusion, it should be noted that the presented monograph is a valuable guide, which can successfully serve the purpose of routine practice in the field of urological pathology in Bulgaria, and would help pathologists in the diagnosis of conventional and rare prostate tumors, as well as in the application of new developments in staging and determining therapeutic management. The monograph written by Dr. Stoeva proves to be an extremely useful scientific work for the daily activities of pathologists, urologists, oncologists, etc., as well as for the training of postgraduate students.

Contributions to the articles included in indicators G7 and G8.

1. **Article with indicator G8.1**. A review article is presented concerning some of the significant changes to the chapter on the prostate gland made in the 2022 WHO classification of tumors of the urinary and male reproductive systems.

A contribution of a **scientific and theoretical nature** is the information on new developments in the classification of tumors of the genitourinary tract, which can be used to update knowledge in this field.

2. **Article with indicator G8.2**. This article details the changes described in the fifth edition of the WHO classification in the sections: intraductal proliferative lesions; treatment-related neuroendocrine carcinoma of the PG; cribriform growth pattern and tertiary Gleason score reporting. The contributions in this article are of a **practical and scientific-theoretical nature**, and new developments in the WHO classification can be used to update knowledge in this area.

Strand 2. Rarely diagnosed diseases.

1. **Article with indicator G.7.2**. Describes a rare case of congenital mesoblastic nephroma of the kidney in an 11-month-old infant diagnosed as a hematoma; rapid recovery after radical nephrectomy, no recurrence; contributions are of **a scientific and practical nature**.

2. **Article with indicator G.7.4.** A rare case of gingival metastasis from colon carcinoma is presented. The poorly known phenomenon of phenotypic transformation from adenocarcinoma to neuroendocrine carcinoma with unusual localization is described. The contributions in this article are of a **scientific and practical nature**.

3.Article with indicator G.7.5. A case of cervical mucocele /ranula/, clinically mimicking a median cyst is discussed. The experience of the multidisciplinary team involved in the diagnosis and treatment of this disease is shared. The contribution of the article is of a **scientific and practical nature**; the focus is on the challenges that arise during the therapeutic process.

Strand 3. Experimental Morphology. 1.Article with indicator G.7.1. An experiment was performed on 4 groups of rats: group I-controls fed standard chow; group II-with food-induced metabolic syndrome/M.S./, and two groups with M.S. and intake of Vit. K1 and K2. No experimental model has been described in the literature regarding the effects of vit. K on morphological changes developing in internal organs; this study contributes to clarify the role of vit. K in M.S., and further studies are recommended to investigate the differences in the described changes; the contributions in this article are of a **scientific and practical nature**.

2. Article with indicator G.7.3. Some of the changes in rat organs in an experimentally established model of vitamin K deficiency are studied. Osteocalcin levels were monitored and materials were taken from the blood vessels of the animals - aorta, pulmonary veins, renal and iliac arteries, and calcium deposits in them were confirmed. The contributions are of an original scientific and practical nature, and relate to:1.A safe dose of warfarin and vit.K has been established, inducing a deficiency state without causing haemorrhages; 2.It has been confirmed that subclinical vit.K deficiency leads to an increase in non-carboxylated osteocalcin and to a decrease in carboxylated osteocalcin; 3. The described model can be used to study the role of osteocalcin in other physiological processes.

Strand 4. Pathology of adipose tissue.

1. **Article with indicator G.8.3.** An autopsy case from the practice is presented, in which the histological changes in the white and brown adipose tissue in the conditions of chronic exposure to cold are examined. The described observations contribute to the understanding of current issues of modern adipobiology; the contributions in the article are of a **scientific and practical nature**.

2. Article with indicator G.8.6. 8 cases of ARVD proven at autopsy are presented. The contributions are of a **scientific-practical nature** and expand the understanding of the observed light microscopic changes in internal organs, while addressing the role of NGF/TrkA and NT-3 TrkC in the onset of myocardial electrical instability in the context of ARVD.

Strand 5. Tumor and non-tumor diseases of the head and neck.

1. Article with indicator G.7.6. A statistical analysis of the relationship between the mean value of the Ki67 marker, the degree of differentiation and survival was performed in a retrospective study of 41 patients with glioblastoma multiforme. The contributions in the article have a **scientific-applied** nature, and the subjectivity of human reporting is avoided by the use of an automated method for counting the positive nuclei in digital histological slides; mean Ki67 values were determined in each individual case; the results of the study contain valuable information in the context of the widespread investigation of the significance of the Ki67 index in malignant diseases of different localization.

2. Article with indicator G.7.7. The reasons for the positive reaction of the IHC-markers AE1/AE3 and EMA typical for epithelial cells in glioblastoma multiforme are discussed; the contribution is of a **scientific-applied nature** and contributes to increasing knowledge of the expression of unusual IXX-markers in glioblastoma multiforme, which is important in the DD of the disease and would prevent a diagnostic error.

3. Article with indicator G.7.8. A comparison was made between the frequency of primary and metastatic intracranial tumors and their distribution by histological variant, gender and age in two separate studies - in 798 cases over a period of 5 years in Bulgaria and 797 cases over 17 years in Brazil. The contributions of the article are of a **scientific and practical nature**, revealing the degree of ethnic dependence in the histological types of intracranial neoplasms. The study, with its total of 1,595 histologically confirmed cases over a total of 22 years in both countries, is the largest in the relevant scientific field at the time of publication.

4. Article with indicator G.7.9. A study was conducted regarding the frequency of histologically confirmed intracranial tumors and their distribution by type (primary, metastatic and other, volume-occupying processes) and histological variant in 822 cases diagnosed over 5 years in two separate medical centers in Varna. The contribution to the study is of an **original nature**, bearing in mind that this is the first such study in Bulgaria, providing detailed information on the researched topic.

5. Article with indicator G.7.10. The study included 619 cases of head and neck tumors, diagnosed in the University hospital "St. Marina" - Varna for a period of 47 months. A detailed analysis of the distribution of tumors by organ localization, histological variant, gender and age was made. The contribution in the article is **original and of a scientific-practical nature**; 1. This is the first in-depth study on the investigated topic, and 2. The published results would support the statistical analysis of head and neck tumors at the national level.

6. Article with indicator G.8.4. A review article is presented that examines problematic diagnostic cases in the field of salivary gland tumor pathology, with an emphasis on basaloid and biphasic tumors. The contribution in the article is of a **scientific-theoretical nature**; several histological types of salivary gland tumors are thoroughly examined with a comparative characterization between them; the article also contains a contribution of a **scientific-practical nature** - the created behavior algorithms are especially valuable for specialists whose field of activity is head and neck tumors.

Strand 6: Molecular mechanisms of carcinogenesis. Article with indicator G.8.5. A review article is presented that examines a little-known transmembrane protein, tetraspanin 151; its structure, its interaction with other proteins and the mechanisms by which it participates in carcinogenesis processes are described in detail. The contribution in the article is of an original **scientific-theoretical nature**; the familiarization of scientific specialists in Bulgaria with the properties of these previously unexamined proteins may lead to the possible "attraction" of interest in them with a view to conducting experiments in connection with their potential as target molecules in oncology.

Strand 7: Infectious Diseases

1. This strand includes a full-text publication in a scientific journal beyond the minimum scientometric requirements for obtaining the academic position of "**Associate Professor.**" The article examines the histological changes in the lungs due to COVID-19 infection, aiming to study the virus's impact on the body and identify potential future complications following the infection. The contributions of the article have a **scientific and practical nature** and are expressed as follows:

The dynamics of histological changes in the lungs have been determined based on the time of occurrence relative to the onset of the disease. 2. Important morphological manifestations of the infection that do not show a temporal dependence on the initial symptoms have been identified. 3The obtained results could help in discovering the long-term consequences of the disease.

II. Teaching Activities

Dr. Martina Stoeva is a Chief Assistant Professor at the Department of "General and Clinical Pathology" at the Medical University of Varna. According to the presented report, Dr. Stoeva's total teaching experience as of November 7, 2024, is 7 years, 1 month, and 4 days. She worked as an Assistant Professor from October 2, 2017, to July 25, 2022, and has been working as a Chief Assistant Professor since July 26, 2022, continuing in this role. Dr. Stoeva actively participates in the education of Bulgarian students in: The Faculty of Medicine, teaching the discipline "General Pathology" to students in the specialty "Medicine" (both Bulgarian and English-language programs). The discipline "Clinical Pathology" for both Bulgarian and English-language students. "Pathoanatomy" for students in the specialty "Dental Medicine" (both Bulgarian and English-language programs). "Pathoanatomy" for students in the Faculty of Pharmacy (Bulgarian-language program) – lectures and practical exercises and for students in the specialty "Medical Laboratory Technician" (Bulgarian-language program). Dr. Stoeva's total teaching hours per academic year are as follows: **2019-2020: 300** hours (10 lecture hours in the Bulgarian-language program and 290 practical hours in the English-language program); **2020-2021: 266** hours (32 practical hours in the Bulgarian-language program and 234 in the English-language program); **2021-2022: 182** hours (14 practical hours in the Bulgarian-language program and 168 in the English-language program); **2022-2023: 152** practical hours (English-language program); **2023-2024: 434** hours (14 practical hours in the Bulgarian-language program and 420 in the English-language program). The report shows that Dr. Stoeva's teaching workload exceeds the required 220 hours for her positions during this period, except for the academic years 2021-2022 and 2022-2023.

III. Medical-Diagnostic Activities

As of November 13, 2024, Dr. Martina Stoeva, PhD, has 7 years, 6 months, and 10 days of professional experience. From May 3, 2017 to November 13, 2024, she has held the following positions: Physician (0.5 FTE); Physician-Assistant (0.5 FTE); Physician-Assistant in "General and Clinical Pathology" (0.5 FTE); Physician-Chief Assistant in "General and Clinical Pathology" (0.5 FTE). She has never interrupted her medical practice and continues to work actively. Dr. Stoeva is highly involved in the overall diagnostic process in the clinic, including autopsy, biopsy, and

cytological diagnostics, demonstrating a strong inclination toward highly specialized activities. Her scientific output is solid evidence of her diverse interests in different areas of medical science.

Conclusion

Dr. Martina Stoeva is a young but already well-established methodical specialist in pathology, possessing clinical and pedagogical experience, deserving of admiration and unconditional support in her challenging professional path. Despite her relatively short professional career, she has mastered many diagnostic methods to perfection, making her an equal partner in collaborative work with colleagues from other specialties.

I believe that Dr. Stoeva possesses all the necessary professional and teaching qualities and fully meets the criteria set by the Academic Regulations of the Medical University of Varna for the position of "**Associate Professor**". Therefore, I strongly recommend her for promotion and urge the esteemed members of the Scientific Jury to vote in favor of awarding Dr. Martina Georgieva Stoeva, PhD, the title of "**Associate Professor**" in the scientific specialty of "General and Clinical Pathology" for the needs of the Department of General and Clinical Pathology, Forensic Medicine and Deontology at the Faculty of Medicine, Medical University of Varna.

19.02.2025

Varna

Assoc. Prof. Dr. Ekaterina Softova -Zlatarova, M.D., PhD