**REVIEW**

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

Scientific specialty "General and Clinical Pathology"; Medical Center "City Lab" EOOD - Varna

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"**, as announced in the *State Gazette*, issue No. 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 the University Hospital "St. Marina" – Varna. According to report No. **102/3334/26.11.2024**, submitted by **Assoc. Prof. Dr. Deyan Jenkov, PhD,** Head of the **Department of General and Clinical Pathology, Forensic Medicine, and Deontology**, as well as the decision recorded in protocol No. **31/02.12.2024** of the Faculty Council of the Faculty of Medicine at the Medical University of Varna, order No. **R-100-929/04.12.2024** in relation to the announced competition, and order No. **R-109-437/05.12.2024** issued by **Prof. Albena Kerekovska, PhD,** Vice-Rector for Academic Affairs of the Medical University of Varna, acting on behalf of the Rector, I have been selected as an external member of the Scientific Jury (SJ). Furthermore, according to protocol No. **1/16.12.2024** from the first meeting of the Scientific Jury, I have been assigned to prepare reviews for the procedure concerning the appointment of an **Associate Professor** in the specialty of **"General and Clinical Pathology."** The candidates for the announced competition are **Chief Assistant Professor Dr. Martina Georgieva Stoeva, PhD,** and **Chief Assistant Professor Dr. Nadezhda Todorova Stefanova, PhD.** As per the established regulations, the candidates have submitted a complete set of materials, both in hard copy and electronic format, including all the necessary documents specified in the **Regulations for the Conditions and Procedures for Acquiring Academic Degrees and Holding Academic Positions** at the Medical University of Varna.

**Brief biographical data and career development of Dr. Nadezhda Todorova Stefanova, MD, PhD**

Dr. Nadezhda Todorova Stefanova was born on December 10, 1986, in the town of Pavlikeni. She completed her secondary education (1998–2005) at "Bacho Kiro" Secondary School in Pavlikeni, specializing in natural sciences and mathematics with intensive English language studies. She was then admitted to the Medical University of Varna, where in 2011 she completed her higher education, obtaining a Master's degree in Medicine (Diploma No. 001477/11.2011, Series MUV No. 000967, issued by the Medical University of Varna).

Dr. Stefanova's professional career began in 2011 when she was appointed as a physician at the Clinic of General and Clinical Pathology at the University Hospital "St. Marina" in Varna. Between 2012 and 2018, she worked as a resident assistant physician at "St. Marina" University Hospital, and on July 20, 2018, after a competitive selection process, she was appointed as a senior assistant physician-resident at the same hospital. From 2019 to 2024, Dr. Stefanova continued to

work as a senior assistant physician and specialist in General and Clinical Pathology at "St. Marina" University Hospital in Varna.

Alongside her professional development, Dr. Stefanova has pursued an academic career. From 2011 to 2012, she was a part-time assistant at the Department of General and Clinical Pathology. In 2012, after a competitive selection process, she was appointed as a full-time assistant in the same department. From 2012 to 2018, she worked as an assistant in General and Clinical Pathology at the Medical University of Varna, and since 2018, she has held the position of senior assistant professor in the Department of General and Clinical Pathology, Forensic Medicine, and Deontology at the Medical University "Prof. Dr. Paraskev Stoyanov" in Varna.

Since 2019, Dr. Stefanova has been recognized as a specialist in General and Clinical Pathology (Certificate No. 022567/01.03.2019, Series MUV No. 4089, issued by the Medical University "Prof. Paraskev Stoyanov," Varna). By order No. R-109-167/17.05.2016 of the Rector of the Medical University of Varna and a decision of the Faculty Council of the Faculty of Medicine, Dr. Stefanova was enrolled as an independent doctoral student in the Department of General and Clinical Pathology, Forensic Medicine, and Deontology at the Medical University of Varna. By order No. R-109-365/23.10.2017, she was granted the right to defend her dissertation.

On February 16, 2018, Dr. Stefanova successfully defended her dissertation titled "Expression of Markers for Autophagy and Necroptosis in Colorectal Carcinoma", obtaining a Ph.D. degree in General and Clinical Pathology (Diploma No. 371/21.05.2018).

Dr. Stefanova has an impressive list of diplomas and certificates for participation in numerous courses, individual training sessions, and seminars (a total of 15), five of which were conducted between 2015 and 2022 at the "European School of Pathology" on various medical topics. Among these, notable training sessions and seminars focused on gynecological pathology, thyroid pathology, male urinary tract pathology, neuroendocrine neoplasms, breast tumors, brain tumors, and the application of the TNM classification in clinical oncology. Dr. Stefanova also holds a certificate for completing a qualification course on "Pedagogical Foundations of Academic Teaching," under Project No. BG051P0001-3.1.09-0013, titled "Creating a Modern Career Development System for Lecturers at the Medical University of Varna."

Dr. Stefanova has authored 33 articles published in national and international journals, totaling 242 pages. She has participated in 23 national scientific forums with published abstracts, 4 international scientific forums with published abstracts, and 4 additional presentations in Bulgaria and abroad (including a poster presentation in Barcelona, Spain, and an academic lecture in Porto, Portugal, in 2024). Among these, she is the first author in 8 publications, the second author in 4 publications (2 of which are international), the third author in one publication, and a co-author in 10 more. Some of her publications are indexed in internationally recognized databases such as Web of Science and Scopus.

Dr. Stefanova has presented at a total of 27 national and international scientific forums, delivering 9 oral presentations and 14 poster presentations. In international scientific events, she has given 1 oral presentation (in the Czech Republic in 2018, co-authored with a research team) and 3 poster presentations at a congress in 2024 in Kemer, Antalya, Turkey. Her report titled

"Mediterranean Spotted Fever in a 45-Year-Old Man", presented in 2008, won 2nd place at the Sixth International Medical Science Conference for Students and Young Doctors in Pleven, Bulgaria (October 15–18, 2008).

Dr. Stefanova has been part of the research teams for 8 scientific projects—7 funded by the "Science" Fund at the Medical University of Varna and 1 funded by the "Scientific Research" Fund. She has B2-level proficiency in English and excellent computer skills. She is a member of The Bulgarian Medical Association (BMA), The Bulgarian Society of Pathology, The European Society of Pathology, The Union of Scientists in Bulgaria – Varna Branch

**Evaluation of scientometric indicators in relation to participation in a competition for the academic position of "Associate Professor"**

**1. Research Activity:** The overall publication activity of Dr. Nadezhda Stefanova, Ph.D., consists of 24 scientific works reflecting her research activity during the period 2016–2024, to which are added three additional publications required for obtaining the educational and scientific degree (ESD) "Doctor." For participation in the competition, Dr. Stefanova has presented the following:

- **Doctoral Dissertation**: *"Expression of Markers for Autophagy and Necroptosis in Colorectal Carcinoma."*
- **Monograph**: *"Myeloproliferative Neoplasms: Past, Present, and Future."*
- **Full-text Publications and Reports**, published in scientific journals and collections, excluding those for obtaining the ESD "Doctor," categorized as follows:
    - **Indicator G7**: Publications and reports indexed in globally recognized scientific databases, consisting of 11 articles numbered from 1 to 11.
    - **Indicator G8**: Publications and reports published in non-indexed but peer-reviewed journals or edited collective volumes, consisting of 11 articles numbered from 1 to 11.
- **One additional full-text publication**, exceeding the minimum scientometric requirements for the position of Associate Professor, evaluated at 2.73 points.
- **Three full-text publications** in scientific journals and collections related to obtaining the ESD "Doctor," including one publication in an internationally recognized and indexed journal (WoS/Scopus).

The **doctoral dissertation** on *"Expression of Markers for Autophagy and Necroptosis in Colorectal Carcinoma"* was positively evaluated, fulfilling **Criterion A1** (50 points) from the minimum requirements for the position of Associate Professor according to the Higher Education Act (ZRASRB). The **habilitation thesis (monograph)** secured the required **100 points** for **Criterion B**.

The **total number of points** from **Indicators G7 and G8** for the 22 full-text publications (excluding those for the doctoral degree) is **203.02 points** (minimum requirement: **200 points**), broken down as follows: **113.04 points** from indexed publications under **Indicator G7** (minimum required: **60 points**). **89.98 points** from non-indexed publications under **Indicator G8**. Thus, **Criterion G** from the minimum scientometric requirements for the Associate Professor position is fulfilled.

For the competition, Dr. Stefanova has submitted **four citations** from foreign scientific journals indexed in global scientific databases (WoS/Scopus). According to **Indicators D10-12**, these citations account for **60 points** (each citation in D10 is valued at 15 points, while the minimum required is 50 points). Therefore, **Criterion D is fulfilled.**

**Research contributions and scientific achievements of Dr. Stefanova's scientific works are in the following main areas:**

1. Alternative molecular mechanisms of cell death and cell survival;
2. Diseases of the hematopoietic system
3. Rarely diagnosed diseases
4. Experimental morphology
5. Infectious diseases
6. General biological processes

The review of Dr. Stefanova's contributions in her scientific works highlights the broad spectrum of her scientific and diagnostic interests, as well as the extensive knowledge and skills she possesses. In many cases, practical problem-solving situations arise, requiring competence, responsibility, and an affinity for teamwork—essential for "unraveling" the sometimes tightly bound knot of diagnostic challenges. In this regard, the variety of morphological and immunohistochemical (IHC) research methods used by Dr. Stefanova demonstrate that she is a well-trained specialist who precisely and responsibly interprets research findings. Her approach exhibits a strong inclination toward developing models and algorithms that could aid in the diagnostic process in routine daily practice.

**Contributions related to the main areas in her scientific works:**

**Area 1. Alternative molecular mechanisms of cell death and cell survival**. This group of scientific papers examines the mechanisms of occurrence and the role of alternative types of cell death in tumors. Included in this area are the dissertation—indicator A1, full-text publications from indicators G8.3, G8.7, G8.8, and one additional article beyond the minimum academic requirements. The presented articles demonstrate in-depth knowledge and an appropriate selection of applied research and diagnostic methods.

The contributions in Dr. Stefanova's scientific works can be formulated in two directions: those related to her dissertation and those arising from her publications submitted for academic competition.

**Contributions from the dissertation work: These include I. Two original scientific contributions**, relating to 1. A comprehensive clinico-morphological, molecular-genetic, and IHC characterization of autophagy and necroptosis in colorectal carcinoma patients; and 2. Contribution resulting from the analysis of IHC expression of Beclin-1 and RIP3 with the aim of clarifying the relationship between autophagy and necroptosis with the assessment of some clinic-morphological parameters. A conclusion is drawn that necroptosis induction may be an effective therapeutic strategy in malignant tumor treatment and play an important role in identifying targets and developing new drugs.

**II. Scientific Contributions with Practical Application**, relating to: 1. The high expression of Beclin-1 is identified as a potential prognostic marker for poor overall survival in colorectal carcinoma (CRC) patients; 2. Low cytoplasmic and high nuclear expression of RIP3 is associated with low survival rates in CRC patients; 3. The expression of autophagy and necroptosis markers was analyzed in relation to clinico-morphological indicators and overall survival in these patients; 4. The profile of patients with an increased risk of fatal outcome from CRC was determined based on clinico-morphological characteristics, IHC expression of Beclin-1 and RIP3 - markers for autophagy and necroptosis.

**Contributions in publications by indicators:**

**Article from indicator G.8.3.** A retrospective analysis was conducted of 98 patients with metastatic colon carcinoma who underwent first-line 5-FU-based chemotherapy at St. Marina University Hospital in Varna. 1. The performed Cox regression analysis, which has a scientific and original contribution, shows that patients with high expression of Beclin-1 tend to have an increased risk of disease progression. 2. **Scientific-practical contribution** – it has been established that colorectal cancer patients with high expression of Beclin-1 are associated with a higher rate of progression when treated with first-line 5-FU-based chemotherapy.

**Article from indicator G.8.7.** – a literature review has been conducted on necroptosis as an alternative mechanism of cell death in various types of malignant diseases; the main signaling pathways of necroptosis have been summarized, specifying the types of malignant diseases in which this type of cell death has been identified. **The contribution of the article is of a scientific-theoretical nature.**

**Article from indicator G.8.8.** A literature review was conducted, highlighting the dual role of the autophagy marker Beclin-1 in biological cellular processes during tumorigenesis - a contribution of a scientific and theoretical nature;

Article beyond the minimum scientometric requirements for holding the title of Associate Professor; The article examines the essence of the autophagy process, the role of this type of cell death in tumorigenesis, and the main mechanisms that regulate it - the contribution in the article is of a scientific and theoretical nature.

**Area II.** Diseases of the hematopoietic system. This direction includes the habilitation/Monographic work - indicator B3, and full-text publications with indicators: G.7.9; G.8.1; G.8.4; G.8.9; and G.8.11.

**Indicator B3. Monographic work** on the topic: "Myeloproliferative neoplasias. Past, present and future." The monograph contains **contributions of a certain scientific-theoretical and scientifically original nature.** The work is written on 191 pages and illustrated with 36 high-quality, informative figures taken from the study of original material, as well as 30 tables. A comprehensive literature review has been conducted, clarifying the nature of Philadelphia-negative MPNs. The epidemiology, risk factors, and pathogenic mechanisms of MPNs are described. The main steps in the diagnostic process and the challenges associated with it are summarized. The nosological entities PV, ET, and MF are sequentially presented, highlighting their general

characteristics, clinical presentation, laboratory findings, and diagnostic challenges, as well as prognosis and treatment. The evolving morphological changes in the bone marrow in the three types of MPNs are examined in detail, emphasizing the fact that bone marrow examination remains essential for assessing changes throughout the course of the disease.

**Article with indicator G.7.9.** The influence of JAK2 V617F- allele load and changes in leukocyte count on the development of thrombotic events in patients with PV and ET is monitored. **The contribution in the publication is of scientific-original and scientific-applied nature.** No correlation was found between higher levels of allele load and the frequency of TS, and patients with higher load had more pronounced splenomegaly; a significant correlation was found between leukocytosis and the presence of splenomegaly.

**Article with indicator G.8.1.** The expression of VEGF in patients with newly diagnosed NHL, their relationship with clinicopathological characteristics and prognostic parameters was studied; **the contribution in the article is of a scientifically original nature.**

**Article with indicator G.8.4.** A study conducted in 318 patients with MPN diagnosed in the period 2008-2017 is presented, with the aim of determining the frequency and prevalence of the JAK2 mutation in patients with Philadelphia-negative MPN; **the contribution in the article is of a scientifically original nature;** the data from the study provide better information about the frequency of the mutation in patients with PN-MPN among a part of the Bulgarian population;

**Article with indicator G.8.9. The contribution in the article is of a scientific and theoretical nature;** the changes and updated diagnostic criteria in the revised WHO classification of MPN from 2016 are described.

**Article with indicator G8.11.** The main driver mutations in MPN are described, as well as the intracellular signaling pathways activated by them, involved in the pathogenesis of the diseases; **contribution of a scientific and theoretical nature;**

**Area III. Rarely diagnosed diseases.** The group includes scientific works with indicators G.7.1; G.7.4; G.7.6; G.7.7; G.7.8; the articles presented in this direction have mainly **scientific and practical contributions,** as they describe interesting and rarely encountered cases in clinical practice; in one of the articles (G.7.1.) a case of a patient with a very rarely developing, but with an aggressive course of the disease anorectal melanoma, diagnosed in the second stage, is reported, describing the pathomorphological findings and mutational status, as well as their relationship with the clinical behavior of the tumor and the prognosis for the patient; in another article (G.7.4.) a rare inflammatory fibroid polyp of the duodenum is reported, discussing DD and emphasizing the role of IHC examination in differentiating the polyp from other similar lesions; the contribution in the article is of a scientific and applied nature;

**Article with indicator G.7.6.** A rare case of spinal paraganglioma is presented; the histological and IHC findings and the difficulties in making the diagnosis are described; **the contribution is of a scientific and practical nature;**

**Article with indicator G.7.7.** The article presents a rare pancreatic tumor, occurring mainly in young women; in this case, the tumor developed in an older patient; attention is drawn to the need to consider chronic granulomatous inflammation and indurative pancreatitis in the DD, for which CT and PET/CT imaging studies are required.

**Article with indicator G.7.8.** A case of primary NHL of the thyroid gland is described, presenting the possible challenges in the diagnosis, treatment and prognosis of this rare lesion; **the contribution is of a scientific and practical nature.**

**Area IV. Experimental Morphology.** This is the group with the largest number of scientific papers, including articles with indicators G.7.2; G.7.5; G.7.10; G.7.11; G.8.5; G.8.6; and G.8.10 from the academic reference.

**In an article with indicator G.7.2.** The protective effect of melatonin in an experimental model of gastric lesion induced by burns was studied; it is emphasized that thermal trauma leads to oxidative damage to the gastric mucosa; melatonin exhibits a gastroprotective effect by activating Nrf2, weakening lipid peroxidation and modifying the Bax/Bcl2 ratio; **the contribution is of scientific original nature;**

**In an article with indicator G.7.5.** A comparison of three modified methods for RNA extraction from formalin-fixed and paraffin-embedded biopsy tissue processed by different strategies for cDNA synthesis/complementary DNA/ was carried out. It was found that the combination of lysis buffer with phenol-based extraction gives a higher yield of RNA; preliminary amplification of the template increases the sensitivity of the analysis; **the contribution in the article is of a scientific-applied nature.**

**In an article with indicator G.7.11.** The effects of the flavonoid fustin, isolated from the wood of Cotinus coggygria, were studied in a model of paracetamol-induced liver damage; the hepatoprotective effect of the flavonoid fustin was demonstrated in an experimental model of acute paracetamol-induced liver toxicity in rats; **contribution of scientific originality;**

**In an article with indicator G.8.5.** The expression of CK 19 in follicular adenoma of the thyroid gland was monitored; absent or focal and moderately expressed cytoplasmic expression of the marker was found, combined with the lack of changes in microvascular density; **the contribution in the article is of a scientifically original nature.**

**In an article with indicator G.8.6.** The expression of NP-1 in patients with metastatic clear cell renal cell carcinoma was monitored; it is assumed that high levels of its expression play the role of an independent factor in predicting incidents related to adverse disease development in these patients; **the contribution in the article is of a scientifically original nature.**

**In an article with indicator D.8.10.** The effect of the flavonoid fustin in a model of indomethacin-induced gastric ulcer was studied. It was found that pretreatment with fustin slightly reduces macroscopic indicators of gastric damage and the severity of histological indicators; fustin exerts a gastroprotective effect in a model of indomethacin-induced gastric ulcer, probably related to its anti-inflammatory activity; **contribution of scientific-original nature.**

**Area V. Infectious diseases.**

**Article with indicator G.7.3.** A study was conducted on 27 autopsy cases of COVID-19 proven by rtPCR, in which an analysis of the morphological changes in the lungs was made in relation to the duration of the disease at the time of death. The dynamics of early and late changes in the lungs in the disease were determined, and the probability of long-term and severe complications in patients with post-covid syndrome was also noted; **a contribution of a scientific and practical nature.**

**Area VI. General biological processes.** This direction includes one article that focuses on the role of the thymus and pineal gland in the course of physiological processes in the human body.

**Article with indicator G.8.2.** A literature review of published data on the relationship between the thymus and the pineal gland and their role in the course of physiological processes in the body has been made. It has been established that the thymus - pineal endocrine axis plays an important role in normal and pathological conditions in the human body. It is important not only for maintaining the immune response, but also for regulating aging and the occurrence of age-related conditions and diseases; **a contribution of a scientific and theoretical nature.**

**II. Educational and teaching activities.**

Dr. Nadezhda Stefanova is a Chief Assistant Professor in the Department of "General and Clinical Pathology, Forensic Medicine, and Deontology" at the Medical University of Varna. According to the submitted report, as of October 29, 2024, her total teaching experience is 12 years, 8 months, and 14 days. Dr. Stefanova worked as an Assistant Professor at the university from February 14, 2012, to August 19, 2018, and has been a Chief Assistant Professor since August 20, 2018, continuing in this role to the present.

Dr. Stefanova actively participates in the education of Bulgarian students in the Faculty of Medicine, teaching "General Pathology" to students specializing in Medicine (both Bulgarian and English language programs); "Clinical Pathology" (both Bulgarian and English language programs); "Pathological Anatomy" to students in the Dentistry program (both Bulgarian and English language programs); "Pathological Anatomy" to students in the Faculty of Pharmacy (Bulgarian program – lectures and practical exercises); and "Medical Laboratory Technician" (Bulgarian program).

During the 2019-2020 academic year, her total teaching workload was 316 hours—90 hours of lectures and practical exercises for the Bulgarian program and 226 hours for the English program. In 2020-2021, she taught 24 hours in the Bulgarian program and 226 hours in the English program, totaling 250 hours. In 2021-2022, her workload included 37 hours in the Bulgarian program and 274 hours in the English program, totaling 311 hours. In 2022-2023, she taught 34 hours of practical exercises in the Bulgarian program and 306 hours in the English program, totaling 340 hours. For the 2023-2024 academic year, she conducted 16 hours of practical exercises and 2 hours of lectures in the Bulgarian program and 394 hours in the English program, totaling 412 hours. The report shows that Dr. Stefanova's teaching workload significantly exceeds the

required 220 hours for the positions she has held during this period. Additionally, she served as a course leader for fourth-year English-language students from 2016 to 2023.

**III. Clinical and Diagnostic Activity**

As of October 22, 2024, Dr. Nadezhda Stefanova, PhD, has a total professional experience of 13 years, 0 months, and 17 days. Throughout this period—from October 5, 2011, to October 22, 2024—she has progressed through various roles, starting as a physician in a 0.5 FTE position, then working as an assistant physician, a resident physician, and eventually a Chief Assistant Professor and specialist in the Clinic of "General and Clinical Pathology" at University Hospital "St. Marina" – Varna.

Dr. Stefanova is actively involved in the entire diagnostic process conducted in the clinic, including autopsy procedures, histological and cytological biopsy diagnostics, as well as highly specialized investigations of carcinomas from various anatomical locations (stomach, lungs, head and neck tumors, prostate, thyroid gland, etc.). Her professional interests are primarily focused on oncological diseases, with an emphasis on lymphoproliferative and hematopoietic malignancies. She has a strong affinity for the application of molecular pathology in the diagnosis of oncological diseases.

I have known Dr. Stefanova from the very beginning of her professional career and have an excellent impression of her overall demeanor, professional ethics, sense of responsibility, and willingness to offer selfless assistance in difficult situations. She is a responsible individual, a respected and well-prepared specialist—young but highly capable of working in a team, with a strong desire for continuous professional development. The scientific work she has presented is evidence of her diverse interests in various medical fields.

I firmly believe that Dr. Stefanova fully meets the requirements and criteria, as well as the quantitative scientometric indicators set in the Academic Staff Development Regulations of the Medical University of Varna for the academic position of "Associate Professor." In light of all this, I confidently give my positive evaluation and recommend that the esteemed members of the Scientific Jury vote in favor of awarding Dr. Nadezhda Todorova Stefanova, PhD, the academic title of "Associate Professor" in the scientific discipline of "General and Clinical Pathology.

14.02.2025

Assoc. Prof. Dr. Ekaterina Softova-Zlatarova, MD.