STATEMENT

Assoc. Prof. Neli Stefanova Petrova, MD, PhD

External member of the scientific jury

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Regarding the Dissertation Thesis

of **Paola Nikolay Kulicheva, MD**

entitled:

"Predictive Factors for Mortality in Young and Middle-Aged Patients

with Ischemic Stroke"

submitted for the award of the **educational and scientific degree "Doctor"**

in Higher Education Area **7. Healthcare and Sports,**

Professional Field **7.1. Medicine,**

Doctoral Programme **"Neurology"**

Scientific Supervisor: Assoc. Prof. Darina Kirilova Georgieva-Hristova, MD, PhD

Pursuant to Order No. P-109-476/20.11.2025 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, I was appointed to prepare a review of the doctoral dissertation entitled *"Predictive Factors for Mortality in Young and Middle-Aged Patients with Ischemic Stroke."*

The present review has been prepared in accordance with the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria and the Rules for the Development of the Academic Staff at the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

All stages of the doctoral training have been conducted in compliance with the established regulatory framework. The doctoral candidate has submitted all documents and materials required for the conferment of the educational and scientific degree *PhD*, in full accordance with the institutional regulations of MU–Varna.

I. Brief biographical data and professional development

D-r Paola Nikolay Kulicheva was born on 10 April 1993. She obtained her Master's Degree in Medicine in 2017 at the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

In September 2018, she began postgraduate specialization in Neurology at the Second Clinic of Neurology at St. Marina University Hospital – Varna.

Since 4 November 2020, she has been a full-time PhD student at the Department of Neurology and Neuroscience of the Medical University – Varna. In 2023, she obtained her specialty in Neurology.

She has completed certified training in Doppler sonography (2023).

She is fluent in English and French and is a member of professional organizations, including the Bulgarian Medical Association and the Bulgarian Society of Neurology.

II. Relevance of the topic

The dissertation addresses a highly pertinent and increasingly important clinical problem - the identification of factors predicting mortality in young and middle-aged patients with acute ischemic stroke. In recent years, the growing frequency of ischemic stroke in individuals under 59 years of age has challenged traditional perceptions of age-

related vascular risk and has directed clinical attention toward a population in an active and economically productive phase of life.

The need for a more refined and targeted investigation of predictors of fatal outcome in younger patients arises from the distinct clinical profile and disease dynamics characteristic of this age group. Early identification of clinical, hemodynamic, laboratory, and neuroimaging markers associated with increased mortality has direct implications for the quality of care and for the development of personalized therapeutic strategies.

In this respect, the dissertation topic is not only timely but also of considerable practical relevance, fully aligned with modern neurological practice focused on early risk stratification and optimization of treatment in patients under 59 years of age.

III. Characteristics of the dissertation: volume, content, and structure

The dissertation comprises 174 pages, including 46 figures and 41 tables. It is written in Bulgarian and demonstrates excellent command of specialized scientific terminology. The structure includes the following major sections:

1. Literature Review (42 pages)

The literature review is well structured and reflects a systematic and analytically oriented approach to the research problem. It encompasses eight major thematic sections addressing the pathogenesis, risk factors, and prognostic indicators of ischemic stroke in young and middle-aged adults. The review provides a clear theoretical framework by presenting the definition of ischemic stroke and its etiological classification according to TOAST.

Non-modifiable, modifiable, behavioral, and less frequently documented risk factors are comprehensively examined. Important topics such as patent foramen ovale, acute inflammatory conditions, obstructive sleep apnea, deep vein thrombosis, and malignancies are addressed.

The review further considers prognostic neurological scales (NIHSS, Glasgow Coma Scale), neuroimaging parameters (ASPECTS, lesion localization, hyperdense MCA), hemodynamic values, and essential laboratory markers. The final section discusses treatment modalities and duration of hospitalization.Overall, the literature review is thorough, logically structured, and fully consistent with the objectives of the dissertation.

2. Aim and Tasks (1 page)

The aim is clearly formulated, scientifically justified, and fully aligned with the need to identify predictive factors for mortality in patients under 59 years of age with acute ischemic stroke. Eight research tasks are defined, all coherent and methodologically grounded.

3. Materials and Methods (2 pages)

This section is precise, logically structured, and appropriate for a retrospective clinical study. The dataset consists of a well-defined cohort of 168 patients, divided into target and control groups based on objective criteria. The inclusion and exclusion criteria ensure sample homogeneity, and ethical approval is duly documented.

Clinical, laboratory, and imaging methods are thoroughly described. The use of standardized assessment tools (NIHSS, GCS, ASPECTS) ensures objectivity and comparability. The statistical approach is mature and methodologically sound, employing parametric and non-parametric tests, odds ratios, confidence intervals, and multivariate logistic regression. Model evaluation indices (Hosmer–Lemeshow, Nagelkerke R^2, Omnibus χ^2, classification accuracy) are appropriately applied.

4. Results (57 pages)

The results section provides a methodologically consistent and analytically rigorous presentation of the data. The findings adequately support the objectives of the dissertation and clearly outline the clinical, imaging, and laboratory factors associated with mortality in patients under 59 years of age.

The graphical presentation is concise and precise. The transition from descriptive to univariate and then to multivariate analyses is logical and coherent.

A particularly strong aspect is the structuring of results into twelve analytical domains, covering demographic characteristics, groups of risk factors, TOAST etiology, neurological deficit severity (NIHSS, GCS), vital parameters, imaging markers (ASPECTS, localization, hyperdense MCA), laboratory parameters (leukocytes, CRP, glucose, sodium), treatment type, and hospital stay duration.

The four multivariate logistic regression models (A-D) are well justified and identify independent predictors of mortality. The final model demonstrates balanced selection of variables and high stability.

5. Discussion (24 pages)

The Discussion section is clearly structured and demonstrates the candidate's ability to interpret the findings within the context of established scientific knowledge. All major groups of predictors - modifiable, non-modifiable, behavioral, clinical, imaging, and laboratory are thoughtfully analyzed.

The comparison between the study results and literature data is balanced, logically presented, and contributes to a clear understanding of the prognostic profile in this younger age group.

6. Conclusions and Contributions (3 pages)

Six well-formulated conclusions summarize the research results. Three original scientific contributions are clearly defined and possess both theoretical and practical value.

7. References (22 pages)

The reference list includes 253 sources (6 in Cyrillic, 247 in Latin script) and fully meets the academic standards for a dissertation in vascular neurology.

8. Publications related to the dissertation (1 page)

The candidate has presented two full-text scientific publications directly connected to the dissertation, meeting the normative requirements for PhD degree conferment.

9. Abstract

The abstract, prepared in Bulgarian and English (63 pages; 31 figures; 26 tables), accurately reflects the content and structure of the dissertation.

IV. Critical Remarks

I have no critical remarks.

V. Conclusion

Based on the overall assessment of the dissertation, I conclude that it fulfills all necessary criteria: topical relevance, methodological rigor, clearly established independent predictive factors, and comprehensive critical analysis.

I therefore provide a **positive evaluation** and propose that D-r Paola Nikolay Kulicheva be awarded the educational and scientific degree "Doctor"

15.12.2025

Statement prepared

Заличено на основание чл. 5, §1, б. „В" от Регламент (ЕС) 2016/679

Assoc. Prof. Neli Stefanova Petrova, MD, PhD