

STATEMENT

by Assoc. Prof. Dr. Gergana Hristeva Foreva, MD, PhD

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regarding the dissertation thesis entitled:

“Assessment and Role of Selected Markers of Endothelial Dysfunction and Oxidative Stress in Outpatients with Metabolic Syndrome”

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PhD student at the Department of General Medicine, Medical University – Varna

for the award of the educational and scientific degree **“Doctor”**

in the doctoral programme **“General Medicine”**

1. General Presentation of the Procedure

By Order No. R-109-300/21 August 2026 of the Rector of the Medical University – Varna, I was appointed as a member of the Scientific Jury for the procedure for awarding the educational and scientific degree “Doctor” to Dr. Nikolay Aleksandrov Bekyarov. According to Protocol No. 1/28 August 2026 of the meeting of the Scientific Jury, I was elected to prepare the present official statement.

The set of documents provided to me in hard copy and electronic format was duly compiled in accordance with the applicable regulatory requirements and submitted within the statutory deadline. Upon reviewing the documentation, I found no procedural irregularities. The procedure fully complies with the Bulgarian Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation, and the applicable internal regulations of the Medical University – Varna.

2. Brief Biographical Information about the Doctoral Candidate

Dr. Nikolay Bekyarov was born in 1977. He graduated in Medicine from the Medical University – Varna in 2004. In 2015, he acquired a specialty in Neurology and obtained a Master’s degree in Health Management.

Dr. Bekyarov's professional career has included work in various positions within the healthcare system, including emergency care and outpatient medical settings. This professional experience has contributed to the accumulation of substantial practical knowledge and expertise in the field addressed by the dissertation and has undoubtedly played an important role in shaping the doctoral candidate's scientific interests and research direction.

3. Relevance and General Characteristics of the Dissertation

The dissertation submitted for evaluation addresses a highly relevant and socially significant problem. Metabolic syndrome and the cardiovascular diseases closely associated with it are among the leading causes of premature mortality and disability worldwide, which determines the considerable public health and practical significance of the research.

The dissertation comprises an optimal volume of 104 pages. The text is well illustrated and includes 4 tables and 33 figures, facilitating the presentation and understanding of the scientific information. The bibliography contains 281 references, demonstrating the author's thorough engagement with the current state of knowledge in the field. The structure of the dissertation is balanced and logical and fully corresponds to established academic standards.

4. Knowledge of the Problem

The literature review demonstrates that Dr. Bekyarov has an in-depth understanding of the theoretical and practical aspects of the subject under investigation. The section provides a critical and detailed analysis of the pathophysiological mechanisms underlying endothelial dysfunction and vascular oxidative stress. Particular attention is devoted to redox signalling, transcription factors, and asymmetric dimethylarginine (ADMA) as a key indicator of vascular injury.

Of particular value is the analysis of the protective role of heme oxygenase-1, as well as the comparison between molecular abnormalities and subclinical structural changes assessed by carotid intima-media thickness (CMT). The literature review

demonstrates the doctoral candidate's excellent scientific orientation within the contemporary scientific debate on the subject.

5. Study Methodology

The methodological approach has been carefully designed and is appropriately aligned with the stated aim and eight research objectives. Dr. Bekyarov applies a broad, interdisciplinary range of contemporary methods, including survey-based, biochemical, clinical laboratory, functional, and genetic investigations.

The study population consists of 83 participants divided into two clearly defined groups: patients with newly diagnosed metabolic syndrome ($n = 63$) and clinically healthy controls ($n = 20$). The inclusion and exclusion criteria are objectively formulated. Statistical analysis was appropriately performed using analysis of variance (ANOVA), Student's paired t -test, and correlation analysis. All relevant ethical requirements for conducting biomedical research were observed. The methodology is reliable and provides a sound basis for the validity of the findings.

6. Characterisation and Evaluation of the Dissertation

The aim of the dissertation is clearly formulated and scientifically justified: to assess the role of specific markers of endothelial activation and oxidative stress in outpatients with metabolic syndrome. The eight specific objectives reflect a logical and comprehensive algorithm for the assessment of cardiometabolic risk.

The doctoral candidate successfully supports the thesis that the addition of molecular markers such as ADMA, reflecting endothelial dysfunction, and malondialdehyde (MDA), reflecting oxidative stress, to the standard metabolic profile—including glucose, lipid parameters, and body mass index—may facilitate the detection of vascular abnormalities at an early functional stage, years before the development of irreversible clinical manifestations such as hypertension or atherosclerosis.

The study demonstrates that patients with comparable body mass indices and lipid profiles may nevertheless have substantially different vascular risk depending on the degree of molecular stress.

Of particular importance for clinical practice is the comparison of biochemical findings with imaging-based assessment. This approach makes it possible to distinguish the transition from functional to structural vascular injury. An additional contribution is the investigation of the Nrf2/NF- κ B/HO-1 axis, which provides valuable information about cellular antioxidant capacity and opens up potential opportunities for personalised therapeutic strategies involving agents with pleiotropic effects.

The primary data are presented systematically, critically discussed, and precisely interpreted in the context of the contemporary international literature.

7. Contributions and Significance of the Dissertation for Science and Practice

Following a detailed analysis of the scientific findings, I fully accept the contributions formulated by the author, which are of an original, confirmatory, and applied scientific nature.

Original Scientific Contributions

- For the first time in Bulgaria, the complex interrelationship between the marker of endothelial dysfunction ADMA, the antioxidant enzyme HO-1, and the transcription factors Nrf2 and NF- κ B has been investigated in patients with metabolic syndrome.
- For the first time at the national level, the relationship between early subclinical biochemical abnormalities and carotid intima-media thickness (CIMT) has been analysed, taking into account the delicate balance between factors contributing to vascular injury and endothelial protection.

Confirmatory Contributions

- The pathological changes in the metabolic and atherogenic profiles of individuals with metabolic syndrome compared with healthy controls have been confirmed.
- A directly proportional increase in carotid intima-media thickness with advancing age has been documented in this patient cohort.

- It has been demonstrated that increased ADMA expression as a marker of endothelial activation occurs at a stage preceding measurable structural changes in the vascular wall.

Scientific and Applied Contributions

- It has been demonstrated that assessment of the transcription factors Nrf2 and NF- κ B provides a more reliable and comprehensive picture of endothelial status than the isolated monitoring of individual biomarkers.
- The dissertation outlines potential directions for future therapeutic strategies aimed at modulating the Nrf2 and NF- κ B pathways for vascular protection.
- The proposed diagnostic panel has considerable potential for clinical implementation as a screening tool for the early stratification of vascular risk.

The abstract has been prepared in accordance with the applicable regulatory requirements and provides a relevant and comprehensive reflection of the content, methodology, and contributions of the dissertation.

8. Assessment of the Publications and the Doctoral Candidate's Personal Contribution

Dr. Bekyarov has submitted three scientific publications related to the dissertation, two of which have been published in prestigious journals indexed in the *Web of Science* database. This meets the minimum national requirements for the award of the educational and scientific degree "Doctor".

The candidate's publication activity demonstrates the visibility and recognition of the research findings within the scientific community. Dr. Bekyarov's personal contribution to the planning, conduct, analysis, and preparation of the study is evident, substantial, and leading.

9. Conclusion

The dissertation of Dr. Nikolay Bekyarov, entitled "*Assessment and Role of Selected Markers of Endothelial Dysfunction and Oxidative Stress in Outpatients with Metabolic Syndrome*", represents a completed, independent, and valuable scientific study addressing a relevant medical problem.

The dissertation is characterised by clearly defined objectives, logically structured research tasks, contemporary methodology, and significant contributions of both fundamental and practical relevance to general medical practice.

All of the above provides sufficient grounds for me to give the dissertation a **POSITIVE** assessment and to vote **IN FAVOUR** of awarding Dr. Nikolay Bekyarov the educational and scientific degree "**Doctor**" in the professional field 7.1. Medicine.

Date: 9 September 2026

Place: Plovdiv

Prepared by:

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