

STATEMENT

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Scientific Degree "Doctor"

Regarding: dissertation for the award of the educational and scientific degree **"Doctor"**

Professional field: 7.1. Medicine

Doctoral program: 03.01.39 "Hematology and Blood Transfusion"

Author: **Dr. Svilena Angelova Atanasova** – Assistant in the Department of Internal
Medicine II, FM, MU – Varna

Form of doctoral program: Full-time

TOPIC: "Role of Selected Plasma MicroRNAs as Diagnostic and Prognostic
Biomarkers in Myelodysplastic Syndrome"

SCIENTIFIC SUPERVISOR: **Prof. Ilina Dimitrova Micheva, MD, PhD**

GENERAL PRESENTATION OF THE PROCEDURE AND THE DOCTORAL CANDIDATE

By Order № R-109-148/13.03.2025 of the Rector of MU – Varna, based on the decision of the FC of the FM (Protocol № 36/10.03.2025), I have been appointed as a member of the Scientific Jury for the defense of the dissertation work of Dr. Svilena Atanasova. According to Protocol № 1/25.03.2025, I am assigned to prepare a Statement on the procedure for acquiring the educational and scientific degree "Doctor".

The submitted set of materials (in print and electronic format) complies with the requirements of the Procedure for acquiring the doctoral degree according to the Regulations on Academic Staff Development of MU – Varna. All documents were submitted in accordance with the required procedure.

Dr. Svilena Angelova Atanasova graduated from MU–Varna (2018) with excellent academic performance. She began working as a physician at the Department of Clinical Hematology at University Hospital "St. Marina" – Varna (2018). Since 2019, she has been an assistant for international medical students at MU – Varna, Department of Internal Medicine II. She obtained her specialty in Clinical Hematology in 2024. By order of the Rector of MU–Varna (№ R-109-70/31.01.2020), she was enrolled as a full-time PhD student in the same department with the dissertation topic "Role of Selected Plasma MicroRNAs as Diagnostic and Prognostic Biomarkers in Myelodysplastic Syndrome." She is a member of BMSH and EHA. She has participated in national and international professional hematology conferences and seminars.

RELEVANCE OF THE TOPIC

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal hematological disorders. It is characterized by ineffective hematopoiesis, mono-/bi-/ or pancytopenia in peripheral blood counts, and a variable risk of transformation into acute myeloid leukemia. Current diagnostic practice requires an integrated approach including clinical, morphological, flow cytometric, and comprehensive genetic assessments. There are also conditions associated with cytopenias that mimic MDS. Additional complications may arise from germline mutations, comorbidities, or prior cytotoxic/immunomodulatory treatments leading to dysplastic changes in the bone marrow. The clinical course, including patient survival, shows wide variability.

Although existing international prognostic systems such as IPSS-R and IPSS-M improve risk stratification, a significant proportion of patients remain without clearly defined diagnostic or prognostic markers. The aforementioned serves as a prerequisite for searching for new markers for more precise diagnosis and assessment of therapeutic approaches.

MicroRNAs are part of the epigenetic mechanisms for regulating gene expression – they are non-coding endogenous RNAs of 19–25 nucleotides in length. They actively participate in oncogenesis through various processes that lead to the evasion of angiogenesis, cellular differentiation, apoptosis, and the proliferation of tumor cells. Studying the levels of plasma microRNAs in patients with MDS may contribute to a better understanding of the disease, including the identification of new and practically applicable diagnostic and prognostic markers.

CHARACTERISTICS AND EVALUATION OF THE DISSERTATION

The dissertation consists of 176 pages, containing 29 tables and 19 figures. The literature review includes 290 sources, predominantly from the past five years. The structure of the work is consistent and logical, with proper proportionality maintained between the individual sections, namely: Contents (3 pages), Abbreviations (4 pages), Introduction (2 pages), Literature Review (46 pages), Aim and Objectives (2 pages), Materials and Methods (7 pages), Results (49 pages), Discussion (20 pages), Conclusion (1 page), Key Findings (1 page), Contributions (1 page), Scientific publications related to the dissertation (1 page), References (38 pages).

Literature Review

The literature review includes 290 peer-reviewed sources, providing a comprehensive overview of current scientific data on the topic and outlining the rationale for conducting the present study. The in-depth review demonstrates the author's ability to analyze and synthesize information from various scientific publications, as well as a thorough understanding of the relevance and complexity of the chosen subject.

Aim - clearly formulated and logically connected to the issues discussed in the literature review. It logically leads to the proper formulation of the research **objectives**. It is precisely this coherence between the literature review, aim, and objectives that has enabled Dr. Atanasova to fully develop her topic, demonstrating a multifaceted approach and scientific depth.

Materials and Methods

Dr. Svilen Atanasova utilized data from 40 patients with MDS. This is a prospective study that includes a wide range of clinical, laboratory, and molecular-biological data. A detailed description of the applied methods is provided – ranging from standard diagnostic procedures to quantitative analyses of microRNAs. The statistical processing is based on contemporary methodology and is thoroughly described, which adds to the reliability of the obtained results.

Results

Dr. Svilen Atanasova's results are presented systematically and are excellently visualized. Clear statistical associations were identified between the levels of the five studied microRNAs (miR-22, miR-144, miR-16, let-7a, and miR-451a) in patients with MDS and healthy controls. Threshold values for the microRNAs were established, which may serve to diagnostically distinguish patients from healthy individuals — with miR-451a demonstrating the highest diagnostic potential. Sub-analyses revealed specific associations between the microRNAs and certain clinical and laboratory parameters, including MDS subtype, cytogenetic profile, and R-IPSS risk category. The prognostic potential of the studied microRNAs was not statistically

confirmed within the current sample. Nevertheless, the results highlight the important diagnostic role of some of the analyzed microRNAs (particularly miR-451a). In this regard, the data provide a solid foundation for future research into reliable biomarkers in MDS.

Discussion

In the discussion section, Dr. Atanasova examines the role of each of the five studied microRNAs in the pathogenesis, diagnosis, and potential prognostic value in MDS. She pays particular attention to their associations with clinical and laboratory parameters of the disease. Statistically significant trends are discussed in a structured manner, including: differences in expression between patients and healthy controls, correlations with R-IPSS risk and cytogenetic profiles, the relationships among the microRNAs themselves, their role in the context of non-invasive diagnostics, and their potential prognostic contribution.

The dissertation formulates six main conclusions, aligned with the stated research objectives. The conclusions emphasize the significant downregulation of miR-451a, miR-144, miR-16, and let-7a in comparison to healthy controls, their association with risk stratification, and correlations with various laboratory parameters, including iron metabolism. Special attention is given to the diagnostic relevance of miR-22 and miR-451a, identified as the most powerful biomarkers for distinguishing MDS patients from healthy individuals.

The **bibliography** includes 290 literary sources from international authors, highlighting the relevance of the examined topic and its high scientific value. The selection of publications demonstrates Dr. S. Atanasova's ability to identify and analyze key scientific information.

The dissertation presents **contributions** of both original and confirmatory nature: one of the contributions is reported for the first time in the country, and two are presented for the first time in the available global scientific literature on the subject.

Scientific publications related to the dissertation

The doctoral student has four publications related to the research, two of which list her as first author—evidence of her leading role in conducting the study and preparing the scientific publications. Two of the publications appear in peer-reviewed journals indexed in international scientific databases, while the others - in Bulgarian journals from NRL.

The **thesis summary** provides a concise and systematic overview of the research, with an emphasis on its key aspects. It is presented in 128 pages.

CONCLUSION

The submitted dissertation by Dr. Svilena Atanasova, on the topic of "Role of Selected Plasma MicroRNAs as Diagnostic and Prognostic Biomarkers in Myelodysplastic Syndrome," is relevant and contains important scientific findings with practical applicability. The research work meets all the requirements of the Development of Academic Staff in the Republic of Bulgaria Act, as well as the Regulations for its implementation at the Medical University – Varna. The topic is original – such a focused investigation of plasma microRNAs in MDS has not been previously conducted in Bulgaria and is rarely encountered internationally. The contributions presented in the dissertation possess not only scientific but also potential practical value. The doctoral candidate's publications further confirm the quality of the conducted research. Based on the aforementioned, I consider the submitted dissertation to be relevant, original, and of significant contribution to hematological science and practice. I confidently give my **positive assessment** of the conducted scientific research, as presented in the reviewed dissertation, abstract, obtained results, and contributions, and I recommend that the **esteemed Scientific Jury vote in favor** of awarding the educational and scientific degree "**Doctor**" in the doctoral program 'Hematology and Blood Transfusion' to **Dr. Svilena Angelova Atanasova**.

Date: 23.04.2025 г.

Заличено на основание чл. 5,
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Prof. Dr. Zlatica Grudova-Topova, MD

