

To  
The Chairman of the Scientific Jury,  
determined by Order  
№ P-109-26 / 12.01.2022  
of the Rector of MU-Varna

## **OPINION**

of dissertation for the award of the "Ph.D." title  
From Assoc. Prof. Dr. Zhivka Boneva Asyova, Ph.D.  
Head of the Clinic of Endocrinology and Metabolic Diseases,  
Medical Institute - Ministry of Interior, Sofia,  
external member of the Scientific Jury, appointed by order of the Rector of MU-Varna  
№ P-109-26 / 12.01.2022

**Professional field:** 7.1. "Medicine"; Field of higher education: 7. "Health and sport"

**Doctoral program:** "Endocrinology and metabolic diseases"

**Author:** Dr. Evelina Boykova Zlatanova

**Form of doctoral studies:** independent preparation

**Department:** Second Department of Internal Medicine, Faculty of Medicine, Medical University - Varna

**Topic:** "METABOLIC PROFILE OF PATIENTS WITH HORMONALLY INACTIVE ADENOMAS."

**Supervisor:** Assoc. Prof. Dr. Mira Siderova, MD, MF, MU "Prof. Dr. Paraskev Stoyanov", Varna.

### I. General presentation of the procedure

This opinion has been prepared in accordance with the requirements of the Regulations on the structure and activities of MU-Varna and the Law on the Development of Academic Staff in the Republic of Bulgaria.

The academic set of materials presented by the doctoral student is in accordance with the Regulation for Acquisition of the title "Ph.D." and includes:

- Completed and printed by the doctoral dissertation;
- Abstract;

- Publications and participations related to the developed topic;
- Successfully passed the doctoral minimum;
- Additional materials and documents in accordance with the requirements.

The dissertation was discussed and focused on public defense by the Faculty of Medicine at the Faculty of Medicine - MU - Varna, Protocol № 56 / 07.12.2021

#### Brief biographical reference

Dr. Evelina Boykova Zlatanova was born in Sofia in 1987. She graduated from the Medical University "Prof. Dr. Paraskev Stoyanov "Varna in 2011 with full honors and a Golden Hippocrates Award. Since 2011 she is part of the team of the Clinic of Endocrinology and Metabolic Diseases of the University Hospital "St. Marina "Varna, where she works so far. Since 2013 she has been a full-time assistant in the Department of Internal Medicine at the Medical University "Prof. Dr. Paraskev Stoyanov " - Varna. Dr. Zlatanova has a degree in Endocrinology and Metabolic Diseases and a Master's degree in Health Management. On 11.12.2018 with Order № P – 109-568 / 25.09.2018. of the Rector of MU – Varna she was enrolled as a doctoral student with an independent form of study at the Second Department of Internal Medicine, Faculty of Medicine, MU - Varna. In the presented CV, the doctoral student indicated a very good command of the English language.

#### III. Relevance and significance of the topic

The presented dissertation is dedicated to a problem concerning the challenges in the diagnosis and approach to hormonally inactive adrenal adenomas. In recent decades, this topic has become increasingly relevant due to the widespread use of modern visualization techniques. Thus, when performing these tests, due to gastroenterological, nephrological or surgical problems, they are "accidentally discovered", the so-called "incidentalomas". The European Society of Endocrinology Clinical Practice Guideline (2016) states that 3-7% of people over the age of 50 have adrenal tumors, and about 75% of incidental tumors are non-functioning adenomas. Hormone-secreting adrenal adenomas as well as subclinical cortisol-secreting adenomas have been shown to be associated with increased metabolic and cardiovascular risk. The relationship between non-secreting adrenal adenomas and metabolic abnormalities has been studied poorly, but is of increasing interest to researchers and is the subject of this paper.

#### IV. Structure of the dissertation

The work I got acquainted with proves the existence of a clearly defined profile of scientific interests, specific scientific tasks and working hypotheses.

The presented scientific work is written on 126 pages and includes: introduction - 3 pages; literature review - 47 pages; purpose and tasks - 1 page, material and methods - 5 pages, results and discussion - 60 pages, conclusions - 2 pages, conclusion and contributions - 4 pages. The bibliographic reference is 25 pages and contains 250 titles, from which 13 in Cyrillic, the remaining 237 - in Latin. The coverage of Bulgarian sources on the issue makes a positive impression.

The literary review is detailed and extensive and is entirely topic-oriented. The review covers all aspects of the given topic and logically presents the arguments for conducting the research. It reflects the good scientific training and knowledge on the problem of Dr. Zlatanova. It is

supported by appropriate literature sources, as 127 of the sources (61.3%) in the bibliography are from the last 10 years, and 16 (6.4%) are from the last 5 years, which shows good awareness of the doctoral student for theoretical discussion on the topic in modern science. literature. The aim is formulated specifically, clearly and precisely in order to analyze the diagnostic, metabolic, biochemical and hormonal aspects of patients with hormonally inactive adrenal adenomas.

To achieve this goal, 6 tasks are set, which derive from it and allow the comprehensive development of the study: 1) Determining the frequency of metabolic syndrome, its components and their relationship with anthropometric indicators; 2) Examination of serum cortisol, rhythm, urinary cortisol, express blockade with 1 mg. dexamethasone, aldosterone / renin ratio, metanephrines and their relationship to adenoma size; 3) Comparison of the frequency of metabolic disorders between patients with non-functioning incidentalomas and the general Bulgarian population; 4) Determining the relative share of newly discovered glycemic disorders and the role of insulin resistance in dysfunctional incidents; 5) Study of fatty liver index, liver enzymes and their correlation with the size of the adenoma; 6) Development of a diagnostic algorithm for searching for metabolic disorders in patients with dysfunctional incidentalomas.

Methodology of the study: the study was originally designed, covering a Bulgarian population of 105 patients with hormonally inactive adrenal adenomas. Specific inclusion and exclusion criteria have been formulated, ethical requirements have been met and clinical, imaging and statistical methods have been used. The results and the discussion are summarized in 60 pages with 32 figures and 37 tables included in the text, which perfectly illustrate the obtained data. The results are clearly structured and demonstrate compliance with the set tasks and support for the set working hypothesis. A number of modern statistical methods have been used to process the data from the studied groups, which shows that the doctoral student uses them well. The discussion is done together with the results in separate chapters of subanalysis. In each of them the doctoral student objectively compares the obtained own results with data from the scientific literature, which shows the ability of Dr. Zlatanova to analyze, synthesize and interpret scientific information.

The formulated 14 conclusions correspond to the results and cover the overall scientific research. The contributions are 9 and derive from the results obtained and the conclusions drawn. The study is the first in Bulgaria to examine the relationship between hormonally inactive adrenal adenomas and the individual components of the metabolic syndrome and confirms the higher frequency of metabolic abnormalities among patients with hormonally inactive adenomas compared to the general population. I consider it especially valuable that for the first time in Bulgaria the risk factors for the development of metabolic syndrome in patients with hormonally inactive adrenal adenomas have been identified and an adapted algorithm for assessing metabolic complications in patients with hormonally inactive adrenal adenomas has been proposed.

This would allow early diagnosis of metabolic abnormalities and allow for early preventive measures. That is why I accept the contributions listed and believe that they are of undoubted importance, both scientifically and practically.

#### V. Assessment of the doctoral student's publications and personal contribution

Dr. Zlatanova presents 3 publications: two in Bulgarian and one in a foreign journal, of which she is the first author. The doctoral student has participated in 5 Bulgarian scientific forums in connection with the dissertation.

#### VI. Abstract

The content and quality of the presented abstract are in accordance with the requirements for acquiring the title Ph.D. at MU-Varna and reflects the main results achieved in the dissertation.

#### VII. Critical remarks

I have no critical remarks on the research and the materials presented. Only the Material and Methods section does not specify the type of study and the time period for recruiting patients.

#### VIII. Conclusion

The dissertation I encountered shows that the doctoral student Dr. Evelina Boykova Zlatanova has in-depth theoretical knowledge and professional skills. She demonstrates qualities and abilities to conduct independent research. The dissertation contains scientific and applied results that represent an original contribution to science and meet the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, The Regulations for application of the Law on the Protection of Human Rights and Fundamental Freedoms and the Regulations of the Medical University of Varna. What has been said so far gives me a strong conviction to support Dr. Evelina Zlatanova, believing that she has every reason to be awarded the educational and scientific degree of 'Ph.D.', as well as to recommend the esteemed members of the scientific jury to vote positively for this decision.

09.02.2022

Assoc. Prof. Zhivka Boneva, MD

