To the Chair of the Scientific Jury:
Prof. Violeta Iotova, MD, PhD, DSc
University Multiprofile Hospital for Active Treatment "St. Marina", Varna
Faculty of Medicine, Medical University of Varna
Appointed by Rector's Order No. R-109-405,
Based on the decision under Protocol No. 46/29.09.2025 of the Departmental Council of the Department of Pediatrics and Report No. 103-6377/30.09.2025 of the Dean of the Faculty of Medicine,
Medical University "Prof. Dr. Paraskev Stoyanov" – Varna

REVIEW

by **Prof. Radoslav Yosifov Georgiev, MD, PhD**
Specialty: Diagnostic Imaging
Head of the MRI Unit, Department of Diagnostic Imaging and Interventional Radiology
Faculty of Medicine, Medical University of Varna
Habilitated in the professional field 7.1. Medicine
Appointed member of the Scientific Jury

of the dissertation thesis:

" NONCLASSICAL FORM OF CONGENITAL ADRENAL HYPERPLASIA – A MOSAIC OF THE KNOWN AND UNKNOWN"

submitted for the award of the educational and scientific degree **Doctor**,
professional field **7.1. Medicine**,
area of higher education **7. Healthcare and Sports**,
doctoral program **Pediatrics**

Author: Dr. Teodora Rosenova Karamfilova
Form of doctoral study: Full-time
Department: Pediatrics, Faculty of Medicine, Medical University of Varna
Supervisor: Assoc. Prof. Sonya Galcheva, MD, PhD, Department of Pediatrics, Faculty of Medicine, MU–Varna

1. GENERAL PRESENTATION OF THE PROCEDURE AND THE DOCTORAL STUDENT

The submitted documentation, in both paper and electronic form, fully complies with the Regulations of the Medical University – Varna for the acquisition of the educational and scientific degree "Doctor" and the scientific degree "Doctor of Science" at the Faculty of Medicine. The dossier includes:

1. Dissertation thesis – original in Word and PDF formats
2. Abstract – original in Word and PDF formats
3. Curriculum vitae in European format
4. Diploma and transcript for the degree of "Master of Medicine"

5. Certificate of specialty
6. List of publications related to the dissertation topic
7. Declaration of originality
8. Order of enrollment in the doctoral program
9. Order of completion with right to defense
10. Transcript of the doctoral minimum examination
11. Information forms from the National Centre for Information and Documentation (NACID)
12. Declaration of authorship in accordance with the Copyright Act
13. Application to the Rector for the initiation of the defense procedure

All documents meet the institutional requirements of the Faculty of Medicine, Medical University of Varna.

2. BIOGRAPHICAL DATA

Dr. Teodora Rosenova Karamfilova was born on March 3, 1992, in Kyustendil, Bulgaria. She graduated with honors from the High School of Mathematics "Prof. Emanuil Ivanov". In 2017 she completed her medical studies at the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna. In 2022 she obtained her specialty in Pediatrics. In 2019 she successfully competed for a full-time doctoral position at the Department of Pediatrics, MU–Varna, under the supervision of Assoc. Prof. Sonya Galcheva, MD, PhD.

Over the years, she has participated in numerous international and national training courses, congresses, and symposia. Since 2020 she has served as a part-time assistant lecturer at the Department of Pediatrics, actively involved in the training of students, interns, and residents in both Bulgarian and English.

Dr. Karamfilova has been working as a pediatrician in the Pediatric Intensive Care Unit at the First Pediatric Clinic, UMHAT "St. Marina" – Varna, for over eight years. Since 2023 she has been a resident in Pediatric Endocrinology and Metabolic Diseases, with expected completion in 2026. She has repeatedly received fellowships under the National Program "Young Scientists and Postdoctoral Fellows" of the Ministry of Education and Science of Bulgaria.

Her clinical and research interests focus on congenital adrenal hyperplasia (CAH) – particularly the nonclassical form (NCAH). In 2023 she participated in the Winter School of Pediatric Endocrinology organized by the European Society for Paediatric Endocrinology (ESPE) in Belgrade, where she presented her research project. She is an active member of several professional societies, including the Bulgarian Medical Association (BMA), Bulgarian Pediatric Association (BPA), Bulgarian National Association of Pediatric Endocrinology (BNSPE), Varna Pediatric Endocrinology Society (VAPES) and European Society for Paediatric Endocrinology (ESPE).

3. STRUCTURE OF THE DISSERTATION

The dissertation by Dr. Karamfilova follows the required academic format and includes the following sections: Introduction, Literature Review, Premises, Aim and Objectives, Design, Participants and Methods, Results, Discussion, Conclusions, Summary of Contributions, List of Publications, Appendices, and References.

The thesis comprises 182 pages, illustrated with 36 tables and 11 figures. The bibliography lists 262 references (3 in Cyrillic and 259 in Latin).

The publication record and participation in scientific forums meet the formal requirements for defense. The dissertation is supported by two peer-reviewed publications and four conference presentations, all with Dr. Karamfilova as first author, including presentations at annual ESPE congresses.

Overall, the structure, scope, and individual contribution of the doctoral candidate fully comply with institutional and national standards.

4. RELEVANCE OF THE TOPIC

The research topic is highly relevant and timely. The modern understanding of visceral adiposity as a consequence of androgen excess leading to unfavorable body composition and increased cardiometabolic risk in women with CAH represents a pressing issue in pediatric and endocrine research.

CAH comprimises a heterogeneous group of autosomal recessive enzymatic defects in adrenal steroidogenesis. More than 95% of cases result from deficiency of 21-hydroxylase (21-OH), leading to accumulation of precursors such as 17-hydroxyprogesterone (17-OHP) and excessive adrenal androgen production. The clinical spectrum ranges from severe classical forms in neonates to milder nonclassical variants manifesting later in life.

The nonclassical form (NCAH) was first described by Decourt et al. in 1957, with its molecular-genetic characterization established in 1984 by White, New, and Dupont. It is caused by mutations in the CYP21A2 gene (6p21), resulting in partial (20–70%) enzyme activity and consequently milder, later-onset symptoms, including premature pubarche, hirsutism, acne, menstrual irregularities, anovulation, polycystic ovaries, and impaired fertility, often accompanied by psychological distress.

The author emphasizes the diagnostic challenges and weak genotype-phenotype correlation that complicate clinical management—hence the description of NCAH as a "mosaic of the known and unknown." The study is both scientifically and socially relevant due to the relatively high prevalence, diagnostic difficulties, and the potential to improve quality of life through multidisciplinary care.

5. MATERIAL AND METHODS

The dissertation presents a comprehensive analysis of the clinical, hormonal, and metabolic profiles of adolescent girls and young women with NCAH, focusing on the interplay between these factors and psychological well-being.

The study includes 68 participants—patients with NCAH and age- and BMI-matched healthy controls. The selection criteria and control group are well justified. The methodology includes auxological assessment, evaluation of androgen excess, hormonal and cardiometabolic parameters, glucose and lipid homeostasis, inflammatory markers, and body composition. The statistical analyses are appropriate and ensure reliability of the results.

The data are representative and scientifically sound, fully addressing the study aims and hypotheses.

6. EVALUATION OF THE DISSERTATION

The dissertation comprises 182 standard pages, including a 36-page literature review and detailed presentation of aims, methodology, results, discussion, conclusions, and appendices.

The literature review is extensive, logically structured, and up to date. It provides an excellent foundation for the methodological design and interpretation of results. The rationale for the study is convincingly presented, emphasizing the scarcity of comprehensive investigations into the relationship between chronic hyperandrogenism, metabolic and cardiovascular consequences, and psychological well-being.

The research aim to evaluate cardiometabolic risk, body composition, psychological perception, and quality of life in NCAH patients, and to compare them with healthy controls is clearly defined and appropriately supported by eight specific objectives.

The conclusions are well substantiated by robust statistical analysis, demonstrating the author's deep understanding of the topic.

7. CONTRIBUTIONS AND SCIENTIFIC SIGNIFICANCE

This is the first study in Bulgaria and among the few internationally that comprehensively investigates NCAH in adolescent and young adult females, significantly enriching current understanding of its metabolic and psychosocial implications.

The findings reveal an increased cardiometabolic risk associated with alterations in leptin and adiponectin levels and differences in body composition compared to healthy controls. Importantly, the study demonstrates reduced quality of life and lower psychological self-esteem among NCAH patients, underscoring the need for early diagnosis, multidisciplinary care, and preventive strategies.

The inclusion of validated questionnaires and quality-of-life assessment tools in the appendices provides practical resources for future clinical use.

Overall, the dissertation advances both theoretical knowledge and clinical practice, emphasizing individualized management and holistic care for patients with NCAH.

8. CRITICAL REMARKS AND RECOMMENDATIONS

None.

9. CONCLUSION

The dissertation fully meets the requirements of the **Law on the Development of the Academic Staff in the Republic of Bulgaria**, its Implementing Regulations, and the internal regulations of the Medical University – Varna.

The doctoral candidate demonstrates excellent theoretical knowledge and professional competence in pediatric endocrinology and metabolism, as well as strong research independence.

Based on the presented evidence, I confidently give my **positive evaluation** of the dissertation and the author's contributions, and I **recommend** to the esteemed Scientific Jury to award the **educational and scientific degree "Doctor"** to **Dr. Teodora Karamfilova**.

Date: October 18, 2025
Reviewer: _____
Prof. Radoslav Georgiev
Varna, Bulgaria