

To the Chair of the Scientific Jury:

Prof. Violeta Iotova, MD, PhD, DSc

University Hospital “St. Marina”, Varna

Medical University – Faculty of Medicine, Varna

Appointed by Order No. R-109-405 of the Rector of the Medical University – Varna,

Based on the decision under Protocol No. 46/29.09.2025 of the

Departmental Council of the Department of Pediatrics and the report with Incoming No. 103-6377/30.09.2025

from the Dean of the Faculty of Medicine of the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna, dated 26.10.2024

REVIEW

by **Assoc. Prof. Narcis Nisim Kaleva-Hodzheva, MD, PhD,**

Specialist in Pediatrics and Pediatric Endocrinology,

Head of the Endocrinology Unit, Department of Pediatrics,

University Hospital “St. George” – Plovdiv until the end of 2021,

and Associate Professor at the Department of Pediatrics and Medical Genetics,

Faculty of Medicine, Medical University – Plovdiv

of the dissertation submitted for the award of the educational and scientific degree **Doctor**,
in the professional field **7.1. Medicine**,

area of higher education **7. Healthcare and Sports**,

Doctoral program **Pediatrics**

Author: Dr. Teodora Rosenova Karamfilova

Form of study: Full-time doctoral training

Department: Pediatrics, Faculty of Medicine, Medical University – Varna

Topic: *“Nonclassical Form of Congenital Adrenal Hyperplasia – a Mosaic of the Known and the Unknown”*

Scientific Supervisor: Assoc. Prof. Sonya Galcheva, MD, PhD

1. General Overview of the Procedure and the Doctoral Candidate

The submitted set of materials, both in printed 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 documentation includes:

1. Dissertation – original in Word and PDF formats
2. Author’s abstract – original in Word and PDF formats
3. Curriculum vitae in European format
4. Diploma for the master’s degree in Medicine with transcript
5. Copy of certificate of medical specialty
6. List of scientific publications and papers related to the dissertation topic

7. Declaration of originality
8. Order of enrolment as a doctoral student
9. Order of withdrawal with the right to defend
10. Protocol from the doctoral minimum examination
11. Information cards from the National Centre for Information and Documentation (NACID)
12. Declaration of authorship consent under the Copyright Act
13. Application to the Rector for initiation of the defense procedure

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

2. Biographical Data and Procedural Requirements

Dr. Teodora Rosenova Karamfilova was born on March 3, 1992, in Kyustendil, where she graduated with honors from the High School of Mathematics “Prof. Emanuil Ivanov.” In 2017 she obtained Master`s degree of Medicine at the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna. In 2022 she acquired the specialty Pediatrics.

In 2019, she was admitted as a full-time doctoral student at the Department of Pediatrics, Medical University – Varna, under the supervision of Assoc. Prof. Sonya Galcheva, MD, PhD.

Over the years, she has participated in numerous national and international training courses, congresses, and symposia. Dr. Karamfilova demonstrates strong potential for professional and academic growth in Pediatrics. Since 2020, she has served as a part-time lecturer at the Department of Pediatrics, participating actively in the training of students, interns, and residents, both in Bulgarian and English.

She has worked for over eight years as a pediatrician in the Pediatric Intensive Care Unit at University Hospital “St. Marina,” Varna, where she gained the skills necessary for the preparation and execution of her dissertation research. Since 2023 she has been a Pediatric Endocrinology and Metabolic Diseases resident, with completion expected in 2026.

She has been awarded several times under the National Programme “Young Scientists and Postdoctoral Fellows” by the Ministry of Education and Science of the Republic of Bulgaria.

Her research interests are focused on congenital adrenal hyperplasia – nonclassical form. 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.

Dr. Karamfilova is a member of several professional societies:

- Bulgarian Medical Association (BMA)
- Bulgarian Pediatric Association (BPA)
- Bulgarian National Society of Pediatric Endocrinology (BNSPE)
- Varna Society of Pediatric Endocrinology (VAPES)
- European Society for Paediatric Endocrinology (ESPE)

The dissertation manuscript contains all required structural components: Introduction, Literature Review, Prerequisites, Aims and Objectives, Design, Participants and Methods, Results, Discussion, Conclusions, Summary of Contributions, List of Publications, Appendices, and References.

The dissertation totals **182 pages**, including **36 tables** and **11 figures**. The bibliography comprises **262 references** (3 in Cyrillic and 259 in Latin).

Her **publication activity** and participation in scientific forums meet the requirements of the Medical University – Varna. Two original scientific papers and four conference abstracts (all as first author, including at ESPE congresses) are directly related to the dissertation topic.

The structure of the dissertation and the author's independent contribution fully satisfy the procedural criteria.

3. Relevance of the Topic

The dissertation focuses on the nonclassical form of congenital adrenal hyperplasia (NCCAH) a condition that epitomizes the diagnostic and therapeutic challenges in modern pediatric endocrinology. The very title reflects the complexity of this pathology and the author in her PhD thesis manages to convince us in the adrenal pathology in terms of hormonal deficiency is a "*mosaic of the known and unknown*".

CAH represents a heterogeneous group of autosomal recessive enzymopathies resulting in impaired synthesis of glucocorticoids and/or mineralocorticoids, most commonly due to 21-hydroxylase deficiency (21-OH). This enzymatic defect leads to accumulation of intermediate metabolites and overproduction of adrenal androgens, resulting in hyperandrogenism with a spectrum of clinical manifestations ranging from severe classical forms in infancy to milder, nonclassical variants manifesting later in life.

The nonclassical forms, often undiagnosed for years, are the subject of Dr. Karamfilova's research. The diagnostic difficulties and therapeutic challenges of CAH especially overtreatment or undertreatment have long-term consequences for patients, including infertility, psychosocial stress, and metabolic comorbidities.

In recent decades, increasing attention has been directed toward the quality of life and long-term outcomes of patients with nonclassical CAH, including possible links between chronic androgen excess and metabolic syndrome, insulin resistance, dyslipidemia, hypertension, central obesity, and type 2 diabetes mellitus.

Dr. Karamfilova's work addresses these issues comprehensively, making the topic highly current and significant for both national and international pediatric endocrinology.

4. Knowledge of the Subject

The dissertation is written in correct and precise Bulgarian, with a well-structured and detailed literature review that justifies the choice of topic. The number of studied patients and controls is sufficient, and the statistical analyses are rigorous. The conclusions are logical and demonstrate the author's profound understanding of the problem.

5. Research Methodology

The applied clinical, laboratory, imaging, psychological, and statistical methods are appropriate for the research aims and support the tested hypothesis.

6. Characteristics and Evaluation of the Dissertation and Its Contributions

The dissertation (182 pages) includes a 36-page literature review, followed by presentation of aims, methods, results, discussion, and conclusions, as well as applications and references.

The literature review is concise and focused, highlighting the relevant aspects of the topic. The prerequisites for the study are well-articulated, emphasizing the lack of comprehensive research on the relationship between chronic hyperandrogenism and metabolic, cardiovascular, and psychological outcomes.

The research aim to evaluate the cardiometabolic risk, body composition, psychological perception, and quality of life in females with nonclassical CAH, and to assess their association with clinical and/or biochemical hyperandrogenism compared to healthy controls is clearly formulated.

7. Materials and Methods

The sample size and control group are adequate, matched for age and anthropometric parameters. The described methods ensure reliability and reproducibility of results.

8. Contributions of Dr. Teodora Karamfilova's Dissertation

This is the first comprehensive study in Bulgaria, and one of the few worldwide, to examine nonclassical congenital adrenal hyperplasia (NCCAH) in adolescent girls and young women, thereby substantially expanding current knowledge about this condition. The difficulties in the differential diagnosis (DD) of NCCAH from other hyperandrogenic disorders in females remain a daily challenge in pediatric endocrinology practice. The didactic value of the literature review, together with part of the author's original results, provides insight into these diagnostic challenges and helps to clarify the distinguishing clinical features. The subsequent findings in Dr. Karamfilova's research build upon cases with established diagnosis, revealing a higher cardiometabolic risk, demonstrated by representative parameters, thus emphasizing the importance of prevention and early management. The study elucidates the pathogenetic mechanisms underlying this risk, using leptin and adiponectin levels as indicators, and highlights the differences in body composition between NCCAH patients and healthy controls also contributing to the increased cardiometabolic risk. Equally important is the evaluation of impaired quality of life and reduced psychological self-esteem among NCCAH patients. These findings underscore the necessity for timely diagnosis, adequate multidisciplinary care, and secondary prevention of this relatively frequent condition in adolescence and young adulthood. The dissertation investigates a wide range of clinical and biochemical parameters, some of which are applied for the first time in Bulgaria as part of the assessment of the clinical, laboratory, and body composition profiles of patients with NCCAH. The study demonstrates the impact of chronic androgen excess, in combination with existing adiposity, on the hormonal and metabolic profile of affected young individuals, as well as on their body composition, both

of which are predisposing factors for significant cardiometabolic complications with increasing disease duration.

From a practical perspective, some of the questionnaires, surveys, and quality-of-life assessment tools included in the *Appendices* have potential clinical applicability in everyday practice and across other healthcare institutions. All these contributions are summarized in the author's conclusions: The results of the present dissertation both as novel findings and as confirmation of previously established international evidence demonstrate the necessity of a systematic and comprehensive assessment of the clinical and functional status of patients with NCCAH. Specifically, the integrated evaluation of anthropometric indicators, physical status, metabolic and hormonal profile, body composition, psycho-emotional state, and quality of life should be established as an essential component of routine clinical care for these patients.

9. Publications and Author's Contribution

The presented publications and conference contributions are directly related to the dissertation topic, with Dr. Karamfilova as first author in most cases. Their number and quality meet institutional requirements. The publications disseminate both literature review and original results to the broader scientific community, enhancing the impact of the research.

10. Author's Abstract

The author's abstract, totaling 86 pages, presents the key findings, tables, and figures in a clear and logical manner. It provides a thorough discussion consistent with the dissertation and is sufficiently informative as a standalone document. It fully meets the requirements of the Medical University – Varna.

11. Conclusion

The dissertation includes scientific, scientific-applied, and practical contributions representing original research in the field. It fully meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, its regulations, and the internal rules of the Medical University – Varna.

Dr. Teodora Karamfilova demonstrates profound theoretical knowledge and professional competence in Pediatric Endocrinology and Metabolic Diseases, as well as the ability to conduct independent scientific research.

Based on the above, I confidently give a positive evaluation of the presented dissertation, author's abstract, and related publications, and I recommend to the esteemed Scientific Jury to award the educational and scientific degree "Doctor" to Dr. Teodora Karamfilova.

Date: October 14, 2025

Place: Plovdiv

Reviewer:

Assoc. Prof. Narcis N. Kaleva-Hodzheva, MD, PhD

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
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