STATEMENT

From Assoc. Prof. Dr. Chayka Kirilova Petrova, PhD
Department of Pediatrics, Medical University – Pleven

Regarding: Dissertation of Dr. Nikolinka Yordanova Peykova, full-time doctoral student at the Department of Pediatrics, Medical University - Varna, for awarding the educational and scientific degree "Doctor" in the doctoral program "Pediatrics."

By order of the Rector of Medical University - Varna № P-109-362/28.10.2024, and by decision of the Scientific Jury (Protocol №1/04.11.2024), I have been assigned to prepare an opinion on the dissertation of Dr. Nikolinka Yordanova Peykova titled *"Metabolic Risk and Body Composition in Children Born Small for Gestational Age Due to Genetic Syndromes (Prader-Willi, Silver-Russell, and Others)"* for awarding the educational and scientific degree "Doctor" in the professional field 7.1 Medicine, academic specialty Pediatrics – code 03.01.50.

This opinion has been prepared in accordance with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and the Regulations for its Implementation at the Medical University - Varna.

Biographical Information

Dr. Nikolinka Yordanova Peykova was born in 1990 in Yambol. She graduated from the Mathematics High School in her hometown in 2009. She subsequently pursued her medical education at the Medical University of Varna, obtaining her Master's degree in Medicine in 2015. In 2019, she commenced her doctoral studies as a full-time PhD candidate in the Department of Pediatrics at the same university. Currently, she works as a pediatric endocrinologist at the First Pediatric Clinic of University Hospital "St. Marina" in Varna, where she has been practicing since obtaining her specialty in pediatric endocrinology in 2020. Additionally, she is a part time assistant at the Medical University of Varna within the Academic Educational Organization.

Dr. Yordanova's primary scientific focus is in the field of rare endocrine diseases. She is a specialist in Prader-Willi syndrome under the Endo-ERN network. Since completing her medical studies, she has contributed to two scientific projects at the

Medical University of Varna. In 2022, she completed advanced training at the Erasmus MC Sophia Children's Hospital in Rotterdam, Netherlands, specializing in the care of patients with rare imprinting syndromes, directly linked to her dissertation research. She has participated in multiple scientific symposia, annual meetings under the European Society for Paediatric Endocrinology (ESPE), and has been a recipient of several IPWSO grants for attending international congresses. Her academic contributions include two peer-reviewed articles and two international conference presentations, with her as the lead author in three of these papers.

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1. Assessment of the Relevance of the Topic

Rare diseases are increasingly recognized as a critical area of scientific inquiry due to the paucity of knowledge and the urgent need to develop robust monitoring and therapeutic strategies for affected patients. Imprinting syndromes, such as Prader-Willi syndrome (PWS) and Silver-Russell syndrome (SRS), represent pivotal subjects of investigation, given their shared genetic defect mechanisms yet divergent impacts on body composition and associated elevated risks of early-onset cardiovascular and metabolic complications.

In Bulgaria, there has been no comparable research, and global literature addressing these syndromes remains scarce. This dissertation investigates the metabolic profile and body composition of a substantial cohort of pediatric patients with confirmed diagnoses of PWS and SRS, regularly monitored at an officially designated Expert Center, with significant involvement by the doctoral candidate herself. The findings are poised to expand the knowledge on rare diseases and contribute to the refinement of clinical management strategies for children with PWS and SRS. Consequently, the study is of substantial scientific and clinical importance.

2. Structure of the Dissertation

The dissertation is well-structured, encompassing all essential components across 158 pages.

The **literature review** (37 pages) demonstrates the author's comprehensive knowledge of the researched issues and ability to interpret the sources critically. The candidate has provided an in-depth and detailed analysis of the current understanding of PWS and SRS.

For PWS, the dissertation elaborates on the central nervous system underlying mechanisms of hyperphagia, including the roles of ghrelin, oxytocin, and adipokines (leptin, adiponectin, irisin), as well as sex hormone-binding globulin (SHBG). Attention is given to causes of mortality, endocrine characteristics, and the effects of growth hormone (hrGH) therapy, which lead to improvements in body composition, motor, and cognitive abilities. Key issues such as the risks of obesity, sleep apnea, reduced bone density, and endocrine disorders (hypogonadism, hypothyroidism, hypocortisolism) are also highlighted.

For SRS, the review includes clinical evaluation systems and justifies the use of the Netchine-Harbison Clinical Scoring System. It outlines features such as phenotype characteristics, hypoglycemia, early puberty, treatment with recombinant human hrGH and gonadotropin-releasing hormone (GnRH), metabolic and cardiovascular risks associated with low birth weight, and the role of adipokines in both syndromes.

The **aim and objectives** (1 page) are clearly and succinctly defined. The dissertation is structured around four well-selected objectives aimed at achieving the central goal.

The **design of the study** (10 pages) includes two parallel cross-sectional case-control sub-studies conducted over a three-year period (2021–2023). The study involves 43 children with genetically confirmed PWS and genetically or clinically SRS undergoing treatment with hrGH and GnRH, compared to 39 controls. Participant selection was based on well-defined inclusion and exclusion criteria. Quality of life (QoL) was assessed using a questionnaire adapted for patients with intellectual disabilities. The doctoral candidate actively participated in all aspects of the study.

The **data analysis** was conducted using appropriately selected statistical methods and tests. The writing style is clear, concise, and adheres to high scientific standards.

3. Evaluation of the Results

The findings of the dissertation are scientifically robust and hold significant value. They enrich the understanding of both shared characteristics and distinct specifics in body composition and metabolic profiles associated with the imprinting patterns in PWS and SRS. The results corroborate established patterns in the global literature, highlighting the increased risk of socially significant diseases. Furthermore, they reinforce the necessity of rhGH therapy and tailored care to improve the QoL in these patient populations.

4. Evaluation of Contributions

The contributions of the dissertation are predominantly of an applied scientific nature. The research is clinically oriented and proposes practical markers for assessing increased metabolic risk. It advocates for the routine monitoring of patients with PWS and SRS, providing valuable insights for improving clinical management strategies.

5. Critical Remarks

No substantial weaknesses or ambiguities were identified. All requirements for the preparation of the dissertation have been meticulously observed.

6. Conclusion

The dissertation of Dr. Nikolinka Yordanova represents a thorough and impactful investigation into a pressing and significant issue in the field of rare endocrine disorders, focusing on children with PWS and SRS. This study uniquely provides novel data on the association between waist circumference, high-molecular-weight adiponectin, and the risk of arterial hypertension in PWS patients. Furthermore, it is the first research in Bulgarian children to explore the metabolic profile, body composition, correlations with irisin and leptin levels, and the prevalence of metabolic and cardiovascular abnormalities in these patient cohorts. Additionally, it evaluates the QoL in children affected by these syndromes.

The findings corroborate that SRS patients exhibit metabolic parallels to children born small for gestational age (SGA), necessitating adherence to similar clinical guidelines. The research underscores the imperative need for routine, comprehensive evaluation of metabolic risk factors and body composition in these two rare endocrine disorders. Moreover, the study provides essential evidence for the healthcare system to advocate for the establishment of structured programs, multidisciplinary care teams, and a national consensus for the management of children with PWS. This includes the development of pharmacotherapeutic guidelines tailored to both syndromes.

Through this thesis, Dr. Nikolinka Yordanova demonstrates exceptional theoretical knowledge and professional skills, substantiating her capacity to conduct independent scientific research.

From a scientific perspective, the dissertation fully complies with the requirements outlined in the Bulgarian Academic Staff Development Act (ZRASRB), its

implementing regulations, and the academic development guidelines of the Medical University of Varna.

In light of the above, I provide a highly positive assessment of this dissertation and recommend that the esteemed Academic Jury confer upon Dr. Nikolinka Yordanova Peykova the educational and scientific degree of "Doctor" in the scientific specialty of "Pediatrics" (03.01.50).

November 22, 2024 Prepared by:

Pleven **/Assoc. Prof. Dr. Ch. Petrova, MD/**