STATEMENT

by Prof. Katya Stefanova Kovacheva, MD, Ph.D.,

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Regarding: Public defense of a dissertation for awarding the educational and scientific Ph.D. degree in a doctoral program in Genetics, Professional field 4. 3. Biological Science, Higher Education Field Natural Sciences, Mathematics, and Informatics.

Author: Milena Petrova Stoyanova, MD

Form of the doctoral study: full-time doctoral student /enrolled by Order № P-109-430/16.07.2018/, dismissed with the right to defend by Order № P-109-329/01.08.2022.

Department of Medical Genetics, Faculty of Medicine, Medical University - Varna

Dissertation topic: " Study among Pediatric Patients with Hereditary Pathology Who Received Genetic Counselling

Scientific supervisors: Prof. Lyudmila Boncheva Angelova, MD, PhD

Procedural issues. As per order (№ P-109-329/01.08.2022 and Minutes №1/09.08.2022, I was appointed a member of the Scientific Jury. In this capacity, I am expected to present a statement regarding the defense of a dissertation titled "*Genetic Diagnostic Study among Pediatric Patients with Hereditary Pathology Who Received Genetic Counselling*" for rewarding the educational and scientific Ph.D. degree, Higher Education Field 4, Natural sciences, mathematics and informatics, Professional field 4.3. Biological sciences, Scientific field "Genetics" to the author of the dissertation *Dr. Milena Petrova Stoyanova, MD*, a full-time doctoral student at the Department of Medical Genetics, Faculty of Medicine of Medical University – Varna, with scientific advisor Prof. Lyudmila Boncheva Angelova, MD, Ph.D.

The procedure and the related documents and materials submitted to me are in full compliance with the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for the Implementation of this Law, as well as the Regulations for the Development of Academic Staff of Medical University - Varna.

I declare that I have no joint publications with the Ph.D. student on the topic of this dissertation.

General description of the dissertation. The dissertation consists of 149 pages, divided into sections as follows: introduction (2 pages), review of the literature (35 pages), aim and tasks (1 page), material and methods (9 pages), results (40 pages) discussion (29 pages), conclusion, inferences and contributions (9 pages), list of references (15) and appendices (2 pages). The reference section includes 246 literature sources: 25 in Cyrillic and 221 in Latin alphabet, with 105 (43%) published during the last 5 years. It contains 34 figures, 17 tables, and 1 appendix. The dissertation was prepared at the Department of Medical Genetics, Medical University of Varna, and Laboratory of Medical Genetics, St. Marina University Hospital - Varna. Some of the investigations were partially funded through a scientific research project at Medical University – Varna.

Relevance of the topic. The dissertation presented by *Milena Stoyanova, MD*, addresses health problems of the present day – designing the diagnostic process for genetic diseases and congenital anomalies in children and the role of the clinical geneticist in making an accurate etiological diagnosis and genetic counseling of affected couples in view of risks and reproduction. Genetic (inherited) diseases and congenital anomalies affect 3% to 6% of newborns and are the leading causes of childhood morbidity and mortality. Most of these diseases have an early onset in neonate or infant. The low specific incidence and high clinical and genetic heterogeneity pose problems for their early diagnosis and achieving a precise genetic diagnosis. An accurate etiological diagnosis in such cases is a prerequisite for refining the risks of recurrences, prognosis, treatment options, and antenatal prophylaxis. In recent years, the rapid development of genomic technologies has expanded the possibilities for specific genetic diagnosis by appllying new molecular and genomic tests. In this context, the role of the medical geneticist is of particular importance who, based on his knowledge and genetic expertise, can refer patients for appropriate genetic tests, thus assisting and shortening the diagnostic process. Furthermore, within the framework of genetic counselling, geneticists can provide competent information regarding recurrence risks, treatment options, prognosis, reproductive planning, and prenatal diagnosis. Due to the scarcity of studies in our country on the effects of activities in medical genetic counseling centers with pediatric patients, the research work is particularly significant. The results can help plan and improve genetic diagnostics and facilitate access to specialized genetic services for patients with genetic pathology.

Knowledge of the problem: The literature review (in 4 main chapters) competently presents: the classification, essential characteristics, and epidemiology of hereditary and congenital pathology in childhood; the main methods used in the diagnosis of children with suspected

hereditary disease; genetic counseling as a highly specialized activity in the diagnosis of gene pathology - stages, indications, organization of genetic assistance abroad and in the country; summary.

Aim and tasks: The principal aim is to carry out a descriptive-epidemiological investigation and evaluate the effect of genetic counselling on designing a clinical genetic diagnosis in children with suspected hereditary pathology based on ten years of experience at the University Genetic Centre in Varna. Concerning the set goal, 5 main tasks have been identified, which are well justified and in line with the aim of the study.

Material and methods. This section presents the clinical contingent in detail – 3124 paediatric patients aged 0-18 registered at the University Genetic Centre. The patients were referred to the centre for genetic counselling and/or genetic investigations based on various indications established at other paediatric units. The most important group from a clinical point of view, which was the subject of study in this dissertation, is the selected group of 968 individuals with an unclear preliminary diagnosis, in whom an active diagnostic (laboratory and consultative) approach was applied. The medical genetics specialist plays an active and leading role in making the final diagnosis. The clinical, laboratory methods, specialized software programs, and statistical data processing methods used are described in detail.

Results and Discussion. The results obtained are objective and authentic and correspond to the tasks set in advance. The study data was processed using appropriate methods and well-illustrated in 34 figures and 17 tables. As a result of the applied multidisciplinary approach to diagnose the pediatric patients, of all 3124 registered individuals, a genetic and clinical diagnosis was achieved in a total of 22.3% of them (696 patients): 17.2% with diagnosis confirmed with laboratory tests, 3.8% - with clinically diagnosed syndromes, 1.3% with a single (non-syndromic) congenital anomaly. One of the merits of the dissertation is the evaluation of the effect of the approach providing active medico-genetic activities (a combination of laboratory investigations and counselling). This approach led to the achievement of genetic and/or clinical diagnoses in 34.2% of patients with previously unclear/unproven clinical conditions (10.6% of all patients covered). The doctoral student's results from the study are discussed competently, considering the literature on the subject, indicating the doctoral student's sound knowledge of the subject and the problems associated with diagnosis of this pathology in pediatric patients.

Conclusions. The 5 conclusions (though in too great detail) summarize the results obtained and correspond to the study's aim and tasks set.

Contributions. I recognize the contributions of the doctoral student. Among them, I ascribe particular importance to the fact that the present study is the only scientific work published in our country to evaluate the role of active medico-genetic activity in making genetic and/or clinical diagnoses in pediatric patients. The obtained results and conclusions can serve as a basis for planning medical activities related to hereditary diseases and congenital anomalies.

Evaluation of publications and personal contribution of the Ph.D. student. The main results outlined in the dissertation are summarized and presented in three scientific reports, the Ph.D. student being the first author. Three communications on the dissertation topic were presented at scientific forums (2 in Bulgaria and 1 abroad).

Abstract

The abstract consists of 75 pages and is prepared according to the requirements. The content corresponds to that of the thesis and presents the main elements of the research work.

Conclusion

The dissertation of Milena Petrova Stoyanova, titled "*Genetic Diagnostic Study among Pediatric Patients with Hereditary Pathology Who Received Genetic Counselling*" submitted for my statement is distinguished by the topicality of the subject related to making the diagnosis in genetic diseases and congenital anomalies in persons in childhood and the role of the clinical geneticist in the diagnostic process to achieve an accurate, etiological diagnosis and genetic counseling of the affected families. The dissertation, with its presented results and conclusions, meets all requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for the Implementation of this Law, and the Regulations for the Development of Academic Staff of Medical University - Varna.

I declare my positive evaluation of the scientific work based on the dissertation submitted for a statement.

I recommend the esteemed members of the Scientific Jury to award Dr. Milena Petrova Stoyanova the educational and scientific Ph.D. degree in the scientific specialty "Genetics", Professional field 4.3. 4. Natural Sciences, Mathematics, and Informatics.

11. 10. 2022

Signed:

Prof. Katja Kovacheva, MD, PhD .....