

To the Chairman of the Scientific Jury  
At the Medical University Prof. Dr. Paraskev Stoyanov " - Varna  
Appointed by order № P-109-105 / 17.03.2021  
To the Rector of the University, by procedure

## **PEER REVIEW**

### **OF A DISSERTATION WORK**

of **Krasimira Ivanova Koleva, MD**, entitled 'Some contemporary diagnostic aspects of inflammatory bowel diseases in children and adolescents' for the acquisition of the educational and scientific degree of 'Doctor' in the field of higher education No 7 'Public health and sports', professional direction No 7.1 'Medicine' and scientific speciality of 'Pediatrics'

**Scientific adviser: Assoc. Prof. Miglena Dimitrova Georgieva, MD, PhD**

#### **Reviewer:**

**Prof. Dr. Vanya Nedkova Nedkova-Kolarova, MD**  
**Pediatrician, Head of the Department of Pediatric Diseases and**  
**Head of the Department of Pediatrics at the University Hospital "Dr. Georgi**  
**Stranski"**

**By decision of the Chairman of the Scientific Jury and according to the Order of the Rector of MU-Varna № P-109-105 / 17.03.2021. I am determined to submit this review**

#### **Concise biographical and professional data about the PhD student:**

Krasimira Ivanova Koleva, MD, has been trained at Fifth secondary school of Varna. She graduates in the speciality of medicine from the Professor Paraskev Stoyanov Medical University of Varna in 1994. She has acquired the specialities of 'pediatrics' in 2009 and 'pediatric gastroenterology' in 2016. Since 2017 until presence, she works as assistant in the Department of Pediatrics of the Faculty of Medicine at Professor Paraskev Stoyanov Medical University of Varna. She is a member of the Academic Council of the Medical University of Varna and also a member of ESPGHAN and ECCO.

#### **1. Actuality of the problem**

Inflammatory bowel disease (IBD) is a relatively rare pathology in children and adolescents. The last decade has seen an increase in the relative number of children with newly diagnosed IBD. The social significance of these diseases is determined by the difficult early diagnosis and still insufficiently effective drug treatment in childhood. There is no common diagnostic algorithm, clinical symptoms are diverse, both from the digestive tract and from organs outside the digestive tract, diagnosis is difficult, requiring invasive methods, follow-up is long, sometimes lifelong, treatment is individual, often with combinations of drugs, some of which are expensive with many side effects, the prognosis is not always good. In recent years, many publications on new methods of diagnostics and new schemes of study have appeared in foreign literature. In our country there are single publications on this issue, which determines the relevance of this dissertation.

For all these reasons, the chosen topic of the dissertation is relevant. The introduction of some new diagnostic methods in the field of IBD is important for both clinical work and scientific knowledge.



## **2. Characteristics, volume and structure of the dissertation**

The dissertation of Dr. Krasimira Koleva is developed in 183 pages and illustrated with 99 tables, 12 figures and an appendix. It is written in good Bulgarian, the style is clear, with precise discussion of the data.

The dissertation consists of - content - 2 pages, abbreviations - 1 page, introduction - 2 pages, literature review - 53 pages, purpose, tasks and working hypotheses - 1 page, material and methods - 7 pages, own results - 47 pages, discussion - 34 pages, conclusion - 2 pages, conclusions - 1 page, literature - 27 pages, appendix - 5 pages, list of publications related to the dissertation - 1 page. The list of cited literature includes 227 titles, of which 15 in Cyrillic and 212 in Latin.

The content of the dissertation is well structured and balanced in the separate sections. The list of scientific publications includes 5 articles published in 2020. Dr. Krasimira Koleva is the sole author in one and the first author in 4 articles. The scientific activity of the dissertation is in accordance with the normative requirements.

### **Literature review**

The literature review systematizes the results of research in world literature, published mainly in the last five years on the topic of the dissertation. This testifies to the very good awareness of the doctoral student on the novelties in this issue.

The review emphasizes the clinical importance of HPV in children and adolescents and provides up-to-date and detailed information on the epidemiology, clinical picture, methods for diagnosing Crohn's disease, ulcerative colitis and nonspecific colitis.

When commenting on the epidemiology of IBD, the dissertation pays special attention to the increasing incidence of these diseases in the last two decades and the higher incidence of relapses in the first year of the disease. Clinical manifestations of the digestive tract and extraintestinal manifestations are considered.

The methods of diagnosis are described in detail. The specificity and sensitivity of the methods used are given. They are grouped in three sections - 1 / laboratory tests; 2 / imaging methods and 3 / micro RNAs. In particular, much space is given to the role of microRNAs as a new method for diagnosing HPV. Dr. Krasimira Koleva pays special attention to the accumulated, often contradictory data from separate studies of multiple microRNAs.

The literature review ends with an assessment of the different methods, their comparability, the inability to always give the same diagnostic result. The lack of systematic research on the role of different methodologies entitles the dissertation to conduct the present study.

### **Purpose, tasks and working hypothesis**

The aim of the dissertation is formulated clearly and precisely - to analyze the individualized diagnostic behavior in children and adolescents with IBD with a view to its improvement.

To achieve this goal, the dissertation formulates five main tasks. According to her working hypothesis, the developed original constellation of modern methods for diagnosis and differential diagnosis is quite effective and applicable in children and adolescents with IBD. Particularly important is the 5th task, namely the development of an algorithm for the diagnosis of HPV, which includes microRNAs. This proves the working hypothesis.

### **Material and methods**

The demographic and clinical characteristics of a total of 76 children (41 boys and 35 girls), mean age 13.54 +/- 3.13, with Crohn's disease, ulcerative colitis and nonspecific colitis, hospitalized between 1.I. 2008 and 31.VII.2020 incl. (the study period was 12 years and 7 months). All of them are hospitalized in the Second Children's Clinic at the University Hospital "St. Marina".

The research methods are numerous, divided into 3 groups. - 1 / clinical; 2 / laboratory markers; 3 / imaging studies. Each group of methods consisted of several diagnostic



indicators, which were examined at the time of diagnosis and at the last discharge hospital within the study. The clinical methods are - severity of the disease, assessment of the disease index, number of hospitalizations, number of concomitant diseases and organ localization. Hematological and biochemical methods have been chosen to show the presence or absence of inflammation and iron deficiency. Biological indicators prove inflammation in the intestine. Imaging methods are - abdominal ultrasound, radiography, abdominal scanning, upper and lower endoscopy of the digestive tract and histological examination. Each of these methods has its own diagnostic capabilities and unique limitations.

The statistical methods are chosen appropriately and allow the processing of the obtained data.

### **Own results**

Dr. Krasimira Koleva structures the results obtained in five chapters and five subchapters. They are very well illustrated with figures and a large number of tables. In the first subsection the dissertation presents the systematized results of the established clinical features (severity, comorbidity and organ localization) of IBD. The second subsection covers the laboratory diagnosis of anemia and inflammation by examining hemoglobin, erythrocytes, serum iron, leukocytes, fibrinogen, reactive protein and calprotectin (the latter reporting intestinal inflammation). The results of the study of the expression of 11 microRNAs in some of the patients with Crohn's disease and ulcerative colitis and in 20 healthy controls are also presented here. Such a study is conducted for the first time in the Bulgarian pediatric gastroenterological environment. The results of this study are interpreted in detail and competently by the dissertation.

The third subsection describes the results of imaging studies. They are arranged according to the performed imaging methods (abdominal ultrasound, X-ray examination, scanning examination, upper and lower endoscopy, histological examination).

The fourth and fifth subsections are conclusions according to the first three subsections. In the fourth subsection correlations between the individual indicators are formed. The fifth subsection proposes an original, dissertation work, diagnostic algorithm for children and adolescents with HPV, compiled on the basis of the processed results.

### **Discussion**

This section of the dissertation of Dr. Krasimira Koleva adequately comments and compares the results with those in our and foreign literature.

### **Conclusion**

The conclusion summarizes the most important results of the doctoral student for clinical gastroenterological practice. It is short and clear.

### **Conclusions**

The dissertation ends with seven specific, well-formulated conclusions, which correspond as solutions to the set tasks. The conclusions correctly synthesize the obtained results.

### **Contributions**

I fully accept both the three contributions with original and the four contributions with confirmatory character, which summarize the undoubted significance of the dissertation.

The abstract is developed on 36 pages, structured according to the requirements, and its content fully corresponds to the dissertation.

### **Critical notes**

No significant remarks. There are some repetitions in the literature review and in the discussion.

### **Publications and research**

On the topic of dissertations, Dr. Krasimira Koleva has published 5 scientific articles. She is the sole author of one of the articles and the first of the other four. All articles were published in 2020. This meets the regulatory requirements for the dissertation.

## **CONCLUSION**


The dissertation presented for review is the author's own development, which is

characterized by originality, comprehensiveness and precision. The presented results are of original and contributing character for the practical gastroenterology. The doctoral student Dr. Krasimira Ivanova Koleva has in-depth theoretical knowledge, professional skills in pediatrics and pediatric gastroenterology, as well as qualities and skills for independent research.

Based on my positive assessment of the current dissertation for obtaining the educational and scientific degree "Doctor" in the scientific specialty "Pediatrics", as a member of the Scientific Jury I will vote in favor of Dr. Krasimira Ivanova Koleva.

May 21, 2021  
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Reviewer:

  
*Prof. Dr. Vanya Nedkova Nedkova-Kolarova, Ph.D.*