To the Chairman of the Scientific Jury At the University Hospital Medical Center "N. I. Pirogov" - EAD, Sofia Appointed by order No. RD -26-269/29.01.2025 of the Executive Director of the University Hospital Medical Center "N. I. Pirogov" - EAD, Sofia according to the procedure for filling one academic position "ASSOCIATE PROFESSOR" in "PEDIATRICS" at the Clinic of Pediatric Surgery of the University Hospital Medical Center "N. I. Pirogov" - EAD, Sofia, field of higher education 7. Health and Sports, professional field 7.1. Medicine, announced in the State Gazette No. 90/25.10.2024. upon an approved proposal of the Scientific Council with protocol N ND -01-2-05/15.01.2025 to hold a competition for the position of Associate Professor with a single candidate – Dr. **Denitza Roumenova Kofinova, PhD**

REVIEW

By Prof. Dr. Miglena Dimitrova Georgieva, PhD
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By order No. RD-26-269/29.01.2025 of the Executive Director of UMHATEM "N.I. Pirogov" Dr. Valentin Dimitrov, I am appointed as a member of the scientific jury in connection with a procedure for occupying the academic position of "Associate Professor" in "Pediatrics" for the needs of the Surgery Clinic of UMHATEM "N. I. Pirogov" - EAD, Sofia, with the only candidate Dr. Denitza Roumenova Kofinova, PhD.

By the Protocol of the first meeting of the Scientific Jury, appointed by the above-mentioned order, I am appointed to write a REVIEW on the documents submitted by Dr. Denitza Roumenova Kofinova, PhD.

The submitted documents have been prepared in accordance with the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria, as well as the Regulations on the Development of the Academic Staff of UMHATEM "N. I. Pirogov" - EAD, Sofia.

1.Biographical data

Dr. Denitza Roumenova Kofinova was born on 19.11.1989 in the city of Burgas. She graduated in 2008 in Sofia 125 Secondary School "Prof. Boyan Penev" with a degree in foreign languages with a profile in German. She is fluent in English, German and Russian. In 2014 she graduated with honors from the Medical University of Sofia. From November 2015 to April 2023 she worked at the Clinic of Pediatric Gastroenterology, SBALDB "Prof. Ivan Mitev" Sofia. On 02.11.2015 she started working as a resident physician. In January 2016 she began specializing in pediatric gastroenterology. In 2020 she acquired a specialty in pediatric gastroenterology, and in 2022 - pediatrics. From May 2023 currently a pediatrician, consultant at the Department of Pediatric Abdominal Surgery, UMHATEM "N. I. Pirogov" Hospital. From 2016 to April 2023, he was successively a part-time lecturer, assistant and chief assistant at the Department of Pediatrics, Medical University - Sofia. He teaches Bulgarian and English-speaking students of medicine and dentistry, residents in pediatrics and pediatric gastroenterology and other pediatric subspecialties. He participates in courses organized by the SDO in Pediatric Gastroenterology and Basic Course - Level I.

From 24.03.2016 - 24.03.2020 he is a full-time doctoral student at the Department of Pediatrics. In June 2020, he defended his dissertation on 2D Shear wave elastography on the topic "Assessment of fibrosis in children with chronic liver diseases" at the Department of Pediatrics of the Medical University - Sofia with scientific supervisors Assoc. Prof. Dr. Daniela Avdzhieva-Tzavella, PhD and Assoc. Prof. Dr. Hristo Zhelev, PhD.

In 2020, she received the "Acad. Asen Hadzhiolov" Young Scientist Award in the field of clinical sciences. In 2024, she was awarded the "Doctor of the Year" award in the category "Contribution to the development and application of innovative medicine and unique techniques" for the introduction of a minimally invasive endoscopic procedure for the treatment of gastroesophageal reflux disease (GERD) with STRETTA in pediatric patients at the Children's Surgery - Pirogov.

She is a member of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the Bulgarian Society of Pediatric Gastroenterology, Hepatology and Nutrition (BULSPGHAN), the Bulgarian Pediatric Association, the Bulgarian Association of Ultrasound in Medicine (BAUM), the Bulgarian Academy of Medicine. She is a member of the board of directors of BAUM and deputy editor-in-chief of the journal Diagnostic and Therapeutic Ultrasound.

She has a certificate in abdominal ultrasound - level I and II, conventional gastrointestinal endoscopy. She has completed a course in interventional gastrointestinal endoscopy, to perform STRETTA.

She has completed numerous short-term courses abroad, organized by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), EFSUMB, the American-Austrian Foundation (AAF, OMI Salzburg), EGE University:

1. 3-5 Oct, 2016, 6th International Meeting on Sono-elastography, 2nd Hands -on Course, EFSUMB Ultrasound Learning Centre, Pavia, Italy
2. 18-19 November 2016, EUROSON SCHOOL COURSE – UP-TO-DATE IN LIVER ELASTOGRAPHY, Timișoara, Romania
3. 26-27 January, ESPGHAN Monothematic Conference on PFIC, Budapest, Hungary
4. 27-30 Sept. 2017, ESPGHAN School of Paediatric Liver Transplantation in Bergamo, Italy

5. 28-30 August, 2017 ESPGHAN Danube/Balkan Summer School, Murighiol, Romania
6. 01-03 February 2018, ESPGHAN Monothematic Conference: Management of progressive liver diseases, Brussels, Belgium, Oral presentation: Phenotypic variation in children with MDR3 deficiency.
7. 08-10 March, 2018 ESPGHAN Master Class Coeliac Diseases, Valencia, Spain
8. 14-16 March, 2018 ESPGHAN Master Class Clinical Parenteral Nutrition, Rotterdam, Netherlands
9. 04-05 April, 2019, ESGHAN Monothematic Confrence on Cystic Fibrosis: Gastrointestinal, Hepatologic and Nutritional Aspects, Valencia, Spain
10. 28-30 November 2019, 5th Paediatric IBD Masterclass, ESPGHAN, Malaga, Spain
11. ESPGHAN FUNCTIONAL GASTROINTESTINAL DISORDERS Course December 09–11, 2021 Taormina, Italy, Oral presentation**:** When traditions result in functional dyspepsia
12. OMI Salzburg CHOP Seminar in Pediatric Gastroenterology 12-18.05.2019 Excellent Case presentation: Wilson's disease or not: that is the question?
13. 5-7 May 2022, Childhood Obesity Masterclass, ESPGHAN, Milan, Italy, Oral presentation: GENETIC POLYMORPHISMS IN BULGARIAN CHILDREN WITH NON-ALCOHOLIC FATTY LIVER DISEASE
14. 26-28 January, 2023, ESPGHAN Monothematic Conference: Alagille Syndrome, Athens, Greece
15. 1-3 June 2023, Course Surgical aspects in pediatric gastroenterology, ESPGHAN, Leeds, UK
16. 14-15 December 2023, Nobel Pharma Hematology School for Beta-Thalassemia, EGE UNIVERSITY MEDICAL SCHOOL DEPARTMENT of PEDIATRIC HEMATOLOGY AND ONCOLOGY THALASSEMIA CENTER, Izmir, Turkiye
17. 27-29 June 2024 ENDOSCOPY HANDS-ON COURSE, Athens, Greece, ESPGHAN

2. Academic workload

Dr. Denitza Kofinova has an impressive academic workload: in the specialty "Pediatrics" on the basis of the University Hospital "N. I. Pirogov" - EAD, Sofia, as the head of the practical modules in "Pediatric Gastroenterology" for the period from 02.05.2023 to the present with a teaching load of 315 school days.

3.Main areas of activity

A. Pediatric inflammatory bowel diseases

Pediatric inflammatory bowel diseases (PIBD) - Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis, are immune-mediated conditions that develop in genetically predisposed individuals under the influence of certain environmental factors. They

are socially significant diseases, with a relapsing-remitting course and a disabling nature and a constantly increasing frequency.

Indicators B – 1, 2 report the clinical manifestations, phenotypic characteristics and epidemiological data of Bulgarian pediatric patients over an 8-year period. A total of 90 children with PIBD, 40 with CD and 50 with UC were included in the two publications. In line with the world literature, Bulgarian pediatric patients with PIBD have a more aggressive course of the disease compared to adult patients with PIBD, with involvement of extensive areas of the gastrointestinal tract. The high rate of extraintestinal manifestations – 60% of children with CD and 60% of children with UC – also supports the severe course of the disease. The most common extraintestinal manifestation in both diseases is anemia (indicator B – 1, 2, 4). In a study covering a 10-year period, anemia was observed in 67.5% of the participants, 77.1% of children with CD and 60% of children with UC. Anemia is iron deficiency in 77.8% of patients with CD and 74.1% of patients with UC. Fecal calprotectin is the best surrogate marker for monitoring Bulgarian children with IBD (indicator B – 3). In indicator D 8 – 4, 8 foods and nutritional supplements in children with IBD and recommendations for proper nutrition are reviewed. Risk factors for the need for surgical treatment in children with CD have been found. Female gender ($p = 0.043$), disease behavior ($p = 0.012$) and the presence of perianal involvement ($p < 0.001$) are associated with the need for surgery. Stenosing type of flow (B2) (odds ratio [OR], 24.944; $p = 0.016$), penetrating stenosing (B2B3) (OR, 28.276; $p = 0.011$), and the presence of perianal disease at diagnosis (OR, 95.802; $p = 0.001$) are independent risk factors for surgery. The first results in Bulgaria of children with PIBD treated with tumor necrosis factor alpha inhibitors (anti-TNF alfa) for an 8-year period are reported. Half of the patients were treated with infliximab, 22.9% with adalimumab, and 27.1% of them with more than one biological agent. At the 6th month of treatment, 72.9% achieved clinical remission, and at the 12th month, 47.9% - deep remission.

B. Chronic liver diseases

Chronic liver diseases (CHD) in childhood are an extremely heterogeneous group, the diagnosis and staging of which until recently necessarily included the mandatory performance of a liver biopsy with histological interpretation. In adult patients with hepatitis C (HCV), for the first time, ultrasound examination with elastography as a marker for fibrosis replaced liver biopsy. For the first time in Bulgaria, Dr. D. Kofinova developed a cut-off value of two-dimensional shear-wave elastography (2D-SWE) for significant liver fibrosis (F2) in 53 children with CHD. The study included 13 children with chronic viral hepatitis (hepatitis B – HBV, hepatitis B+D – HBV+HDV; HCV), 9 with autoimmune hepatitis, 13 with non-alcoholic fatty liver disease (NAFLD), 18 with metabolic liver diseases, with various liver diseases, biliary atresia and the presence of a transplanted liver.

Until 2017, the gold standard for the treatment of HCV was pegylated interferon-alpha with or without ribavirin. In 2017, the European Medicines Agency (EMA) approved the use of direct-acting antivirals (DAAs) in children $\geq$ 12 years of age. Indicator G7 - 2 and indicator G8 - 10 review the different HCV treatment regimens over time, as well as current

recommendations for the treatment of HCV in childhood with the new interferon-free regimens. In indicator B – 11, the first cases of children with HCV successfully treated with the DAAs Ledipasvir/Sofosbuvir were reported. 2D-SWE values were compared with the histologically determined degree of liver fibrosis.

With the introduction of genetic studies into everyday practice, the importance of various polymorphisms in the clinical course of various diseases is being discovered. In indicators G 7-10 and G 8 - 3, the role in the progression of liver damage in patients with NAFLD is examined. For the first time in Bulgaria, genetic polymorphisms are being studied - PNPLA3 I148M, GCKR P446L, TM6SF2 E167K in 22 children with NAFLD and 10 healthy controls.

Liver involvement can be observed in various diseases. Indicator G 8-1 examines all liver complications in children with beta-thalassemia, their diagnosis and treatment. Special attention is paid to new non-invasive techniques for the assessment of iron accumulation and liver fibrosis - nuclear magnetic resonance and ultrasound elastography.

In end-stage liver disease, the only therapeutic option is liver transplantation, which is associated with a number of early and late complications and challenges. We share an experience with a 12-year-old girl with a liver transplant due to cirrhosis from congenital biliary atresia, who developed a fibroadenoma of the mammary gland, on the background of immunosuppression with cyclosporine A. The tumor was excised. Immunosuppression was not discontinued or replaced with another drug. Six months later, she was relapse-free (index B – 12).

C. Helicobacter pylori infection

Helicobacter pylori (H. pylori) infection is one of the most common chronic infections that cause gastroduodenitis, peptic ulcer, gastric carcinoma and mucosa-associated lymphoma (MALT). Together with microbiologists, 362 children were examined, 181 with a family history of gastritis complaints and 181 without a family history. The frequency of H. pylori infection was significantly higher in the group of children with a family history of upper gastrointestinal tract complaints (69.1% versus 21.0%, $p < 00001$) (indicator B – 8). Over a period of 7 years, 656 children underwent fibrogastroscopy with histological and microbiological examination for H. pylori, due to various complaints. In 24.5% (161 children) H. pylori was isolated by culture. The relationship between functional abdominal pain, defined according to the Rome IV diagnostic criteria of 2016, and H. pylori was studied. The latter was isolated only in 141 children with functional abdominal pain. No statistically significant relationship was found between H. pylori and functional abdominal pain ($p >0.05$) (indicator D 8 - 11).

D. General pediatric gastroenterological problems

Indicators D 8 - 9, 2, 5, common general pediatric problems such as modern approach and recommendations for infant and young child nutrition, constipation in childhood and the

place of probiotics in pediatric gastroenterology are discussed. Questions that concern every general practitioner and pediatrician.

E. Multidisciplinary Case Reports Indicator B – 9 reports a multidisciplinary approach in the diagnosis and treatment of a 15-year-old girl with a congenital giant epidermoid cyst of the spleen, with complaints of epigastric heaviness and loss of appetite. Laparoscopic splenectomy was performed, which is a challenge in childhood. There were no postoperative complications.

4. Publication activity and contributions

Dr. D. Kofinova's publications are dedicated to current topics - HCV, HCV, PIBD, CLD, H. pylori infection in childhood, functional gastrointestinal diseases and rare diseases in pediatric gastroenterology and pediatrics. Dr. D. Kofinova successfully defended her dissertation in 2020 on the topic "Evaluation of liver fibrosis in children with chronic liver diseases" at the Department of Pediatrics of the Medical University - Sofia with scientific supervisors Assoc. Prof. Dr. Daniela Avdzhieva-Tzavella, PhD and Assoc. Prof. Dr. Hristo Zhelev, PhD. The dissertation is written on 147 standard typewritten pages and is illustrated with 68 tables and 18 figures. The bibliography contains 331 literary sources, of which 8 in Cyrillic and 302 in Latin. The gold standard for determining the degree of liver fibrosis, both in adults and in children, is performing a liver biopsy. The manipulation is invasive, carries risks of complications, in childhood it is necessarily performed under anesthesia, and is also traumatic for children and their parents. The aim of the dissertation is to perform an ultrasound (elastography) and laboratory assessment of the degree of liver fibrosis in children with chronic liver diseases. The dissertation has original and confirmatory contributions. Contributions of an original nature - for the first time in the country, the role of Shear-wave elastography for the assessment of liver fibrosis in pediatric patients has been studied; for the first time in the country, the role of non-invasive blood markers - FibroTest, APRI, FIB-4, ASAT/ALAT for the assessment of liver fibrosis in pediatric patients has been studied; for the first time in the country, the relationship between the values of Shear-wave elastography and liver fibrosis, assessed histologically in pediatric patients with chronic liver diseases, has been assessed; for the first time in the country, the relationship between the values of non-invasive blood markers - FibroTest, APRI, FIB-4, ASAT/ALAT, and liver fibrosis, assessed histologically in pediatric patients with CLD has been assessed; for the first time in the country, a cut-off value for Shear-wave elastography has been found to differentiate fibrosis from the absence of such in pediatric patients with CLD; for the first time in the country, a cut-off value for Shear-wave elastography has been found to differentiate significant from insignificant fibrosis in pediatric patients with CLD; for the first time in the country, a cut-off value for Shear-wave elastography has been found to differentiate advanced fibrosis from the absence of such in pediatric patients with CLD; For the first time in the country, the role of the genetic polymorphisms PNPLA3 I148M, TM6SF2 E167K and GCKR P446L in the development of NAFLD in pediatric patients has been studied; For the first time in the country, an algorithm for monitoring pediatric patients with CLD has been proposed; For the

first time in the country, an algorithm for monitoring pediatric patients with NAFLD has been proposed.

Dr. D. Kofinova has a total of 36 publications, 25 publications in refereed and indexed journals, of which 6 in journals with IF (IF value according to Central Medical Library data - 9.572), participation in 3 textbooks on pediatrics and 6 book chapters published in edited collective volumes. One report with first prize and one poster with second prize. The candidate has citations or reviews in scientific publications, refereed and indexed in world-renowned databases with scientific information or in monographs and collective volumes -10, citations in Bulgarian printed publications, with self-citations excluded - 23.

5. Participation in national and international conferences, symposiums and congresses, international and national projects

Dr. Denitza Kofinova participates in a number of national and international conferences and congresses. Participation in international congresses is 44, in national scientific forums - 52.

6. Memberships

European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN),

Bulgarian Society of Pediatric Gastroenterology, Hepatology and Nutrition (BULSPGHAN),

Bulgarian Pediatric Association,

Bulgarian Association of Ultrasound in Medicine (BAUM),

Bulgarian Medical Association.

Conclusion:

The documentation of Dr. Denitza Roumenova Kofinova, PhD, presented to me for evaluation shows good professional qualities, skills to conduct scientific research, to perform adequate analysis of the obtained results and to draw the relevant conclusions. Dr. Denitza Kofinova is actively engaged with students and postgraduates, as evidenced by the submitted study load report.

I recommend to the esteemed scientific jury to vote positively for a decision - Dr. Denitza Roumenova Kofinova, PhD to take the academic position of "ASSOCIATE PROFESSOR" in the scientific specialty "PEDIATRICS" for the needs of the Clinic of Pediatric Surgery of the UMHATEM "N. I. Pirogov" - EAD, Sofia.

Respectfully submitted:
Prof. Dr. Miglena Georgieva, PhD
03.03.2025г.
Varna