

## OPINION

By Prof. Borislav Georgiev Georgiev, MD, PhD,  
Head of the Cardiology Clinic at the National Heart Hospital  
Member of the Scientific Jury for the Competition for the Academic Position of "Associate Professor" in the Field of Higher Education 7. Health and Sports, professional field  
7.1. Medicine (Internal Medicine), one per half-staff,  
announced in State Gazette No. 37 of 26.04.2024

For the above-mentioned competition, documents have been submitted by two candidates - Dr. Rada Gancheva, PhD and Dr. Nonka Yurukova, PhD. The documents submitted by the candidates are in accordance with the requirements of the regulations for the academic position of "Associate Professor" and the Regulations of Sofia University "St. Kliment Ohridski". I do not find any gaps in the submitted documentation and declare that I do not have common scientific papers with the two candidates.

### 1. Research

#### 1.1. Publications.

Dr. Nonka Yurukova, MD, Assistant Professor at the Department of Internal Medicine, Pharmacology and Clinical Pharmacology, Pediatrics, Epidemiology, Infectious and Skin Diseases of Sofia University "St. Kliment Ohridski" has submitted copies of publications in specialized scientific journals (articles, monographs, etc.), accompanied by a reference for citations, and a reference for publications referenced and indexed in world databases with scientific information. I accept that the Commission on Admissibility of Documents has accepted the distribution of the evidentiary material according to the requirements.

##### 1.1.1. List of publications

Ø PhD thesis on "Metabolic syndrome, Non-alcoholic steatosis disease and cardiovascular complications - diagnosis and treatment"

Ø Published book on the basis of the PhD thesis - Metabolic syndrome, Non-alcoholic steatosis disease and cardiovascular complications - diagnosis and treatment. Sofia, 2022, ISBN 978-619-92274-0-4.

Ø Monograph - Metabolic syndrome, Non-alcoholic steatosis disease and cardiovascular complications. Monograph. Sofia, 2021, ISBN 978-619-188-780-4.

Ø 12 Publications in scientific journals

##### 1.2 Scientific forums.

For the competition, Dr. Nonka Yurukova has listed 4 published texts from participation in conferences and 2 international conferences that she attended without scientific participation.

##### 1.3 Authorship and citations

I did not find data on the total impact factor of the publications for participation in the competition, as well as on the individual impact factor of the candidate.

A reference from the CMB is attached for 1 citation in Bulgarian, 50 citations of publications in indexed and refereed in Scopus and 36 citations in Web of Science, without information about repetitions in both databases and 9 in other foreign open sources. Auto-citations are excluded.

#### 1.4 Participation in research projects

The applicant has participated in an international project Masterclass in organ transplantation - November 2022 - March 2023, credited with 12 EMC credits by the Romanian College of Physicians according to decision No. 1812/01.03.2023. Series B, No. 3/10.03.2023.

## 2. Profile of research, practical and applied activities

The works submitted for participation in the competition are a total of 13.

The main contributions come from the dissertation and related publications.

In the scientific paper "Metabolic Syndrome, Nonalcoholic Steatosis Disease and Cardiovascular Complications – Diagnosis and Treatment", the aim is to determine the importance of Metabolic Syndrome (MetC) and Nonalcoholic Steatosis Disease (NAFLD) for cardiovascular diseases (CVD) and complications and to create a diagnostic-therapeutic model of behavior. The created algorithm for risk assessment for CVD in patients with MetS and NAFLD allows predicting cardiovascular risk using non-invasive assessment markers.

The refined therapeutic algorithm in patients with MetS and NAFLD offers refinement of clinical behavior. As a contribution of an original nature, the demonstration of the importance of NAFLD as an independent risk factor and the creation of a prognostic model for CVD in patients with MetS and NAFLD are taken into account; the creation of a clinical algorithm of behavior in patients with MetS and NAFLD; evaluating the role of NAFLD in patients with Liver Transplantation (HT). As a confirmatory contribution, the confirmation of the importance of the main risk factors for CVD, pro-inflammatory activity for the occurrence of CVD and alcohol and smoking for the development of cardiovascular complications is indicated. The book can be used in patients with Metabolic Syndrome, Non-alcoholic Steatosis Disease and Cardiovascular Disease for effective management of cardiovascular risk.

In the Monograph "Metabolic Syndrome, Non-alcoholic Steatosis Disease and Cardiovascular Complications" the following results are reached: 1. The importance of the main risk factors for CVD is confirmed; of the pro-inflammatory activity for the occurrence of CVD; of alcohol and smoking for the development of cardiovascular complications. 2. The importance of NAFLD as a stand-alone risk factor is demonstrated and a prognostic model for CVD in patients with Metabolic Syndrome and NAFLD is proposed. 3. A clinical algorithm of behavior in patients with Metabolic Syndrome and NAFLD is proposed. 4. The importance of NAFLD in liver transplant patients is evaluated. The monograph is intended for residents and specialists in gastroenterology and cardiology, as well as general practitioners.

The candidate presents data for work in the following areas: Mathematical models for assessing the outcome of liver transplantation in adults and predictive factors for severe Covid-19; Role of T-cells in liver transplantation; Intestinal microbiome, Irritable bowel syndrome and food intolerance, But from the presented evidence there are no significant contributions to these studies with large authors' teams.

## 4. Educational, teaching and scientific-organizational activities

The teaching workload of Dr. Nonka Yurukova, MD, is an assist. Prof. of the Department of Internal Medicine, Pharmacology and Clinical Pharmacology, Pediatrics, Epidemiology, Infectious and Skin Diseases of Sofia University "St. Kliment Ohridski" as follows:

School Year	Hours
2021/2022	440
2022/2023	470
2023/2024 (winter semester)	175

#### **5. PhD students, postgraduate students and diploma students**

The candidate has participated in the training of interns, postgraduates and doctoral students (seminars and practical classes)

#### **6. Reviews**

I did not find any evidence of membership of Dr. Nonka Yurukova to have been a reviewer of national and international scientific journals.

#### **7. Professional skills**

Dr. Nonka Yurukova, MD has a total work experience as a doctor of 27 years and 6 months, of which as an assistant professor 10 years and 10 months. From the scientific research presented, it is striking its almost total commitment to liver transplantation, with minimal interdisciplinary activities. There are additional skills with acquired certificates in Conventional ultrasound – abdominal ultrasound and superficial structures – first level, abdominal Doppler ultrasound – second level and interventional and endoscopic abdominal ultrasound – third level.

#### **8. Membership in scientific organizations**

I did not find any evidence of Dr. Nonka Yurukova's membership in national and international scientific organizations:

According to the minimum national requirements and the requirements of the Regulations on the terms and conditions for acquiring scientific degrees and occupying academic positions at the Faculty of Medicine of Sofia University "St. Kliment Ohridski" and NACID for the academic position of "Associate Professor" Dr. Nonka Yurukova, PhD meets the minimum requirements.

Two candidates have submitted documents for the competition - Dr. Rada Gancheva, PhD and Dr. Nonka Yurukova, PhD. Based on the attached materials, I consider Dr. Rada Gancheva, PhD to be more suitable, based on the interdisciplinary scientific developments and the extremely impressive scientific production and already established international prestige.

In conclusion, I believe that Nonka Yurukova, PhD meets the requirements of the Law on the Acquisition of Scientific Degrees and the Rules of Procedure for Acquiring Scientific Degrees and Occupying Academic Positions at the Faculty of Medicine of Sofia University "St. Kliment Ohridski". But when comparing the two candidates, I cannot support Dr. Yurukova to be awarded the academic position of "Associate Professor" in the field of higher education 7. Health and Sports, professional field 7.1. Medicine (Internal Medicine).

20.08.2024

(Prof. Borislav Georgiev, MD)

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### 1. Research

#### 1.1. Publications.

Dr. Rada Gancheva, MD, Assistant Professor of Rheumatology at Sofia University "St. Kliment Ohridski", has submitted copies of publications in specialized scientific journals (articles, monographs, etc.), accompanied by a reference for impact factor and citations, and a reference for publications referenced and indexed in world databases with scientific information issued by the relevant authorized bodies.

#### 1.1. List of publications

- Ø PhD Thesis on "*Gout and cardiovascular risk*"
- Ø Monograph "*Renal and cardiovascular complications in gout*", (Gancheva R, Kundurdjiev At, Kolarov Zl). Arbilis Publishing House, 2017, ISBN: 978-619-7063-18-9.
- Ø Six published book chapters
- Ø Publications, by group of indicators (First author in 27 publications, second in 8, third in 9 publications, and in the rest subsequent);
  - Publications with IF – 11 posts (total IF – 24.794)
  - Publications in refereed and indexed in Scopus and Web of Science – 40 pcs.
  - Publications in journals referenced in Google Scholar, Crossref, Semantic Scholar – 2 pcs
- ❖ Ø First author of the National Consensus on the Diagnosis and Treatment of Gout;
- ❖ Ø Co-authorship in the international consensus of Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN), published in the *Annals of the Rheumatic Diseases* in 2019 with IF 16.102;

#### 1.2 Scientific forums.

For the competition, Dr. Rada Gancheva has presented

- 22 participations from congresses and conferences with published abstracts in Scopus and Web of Science (11 in Bulgaria and 11 international participations with a total IF – 149.329);
- 17 participations in congresses and conferences with published abstracts in non-refereed editions (9 in Bulgarian sources and 8 in international editions);
- 9 participations in scientific forums, one of them international, without published abstracts.

### *1.3 Authorship and citations*

The total impact factor of the publications for participation in the competition is 24.794, and the individual impact factor of the candidate from publications is 1.814, the total impact factor of published abstracts is 149.329, the individual impact factor of published abstracts is 30.274.

70 citations of publications in indexed and referenced journals in Scopus and Web of Science are attached. Self-citations, hidden self-citations and citations of and in dissertations are excluded.

- Scopus H-index – 4.

### *1.4 Participation in research projects*

- 1) Dr. Rada Gancheva is a Lead Researcher in the research team under Contract No D-23/2013 from the "Young Researcher 2013" competition on the topic: "Study of IL-1 $\beta$ , IL18 and factors of metabolic syndrome in gout".
- 2) She is a Lead Researcher in the research team under Contract No. D-9/2014 of the "Young Researcher 2014" competition on the topic: "Determination of sonographic parameters of kidney, heart, carotids and serum levels of IL-1 $\beta$  and IL18 in patients with chronic gout".
- 3) She is a participant in a research team under Contract No. D-143/24.06.2020 of the "Grant-2020" competition on the topic: "Functional autoantibodies, apoptosis and survival factors of B lymphocytes in patients with an early form of progressive systemic sclerosis".
- 4) She also participates in a research team under Contract No. D-178/14.06.2022 of the "Grant-2022" competition on the topic: "Study of markers of genetic predisposition to systemic lupus erythematosus".
- 5) He is a participant in a research team under Contract No. D-179/14.06.2022 of the "Grant-2022" competition on the topic: "Study of markers of disease activity in the clinical assessment of systemic lupus erythematosus".

## **2. Profile of research, practical and applied activities**

Dr. Rada Gancheva's research activity covers mainly the field of hyperuricemia and gout as cardiovascular risk factors. It was only in 2015 that publications appeared examining the different stages of the disease and especially the appearance of tophi in gout as an aggravating risk factor. Determining the independent importance of hyperuricemia and gout as cardiovascular risk factors is problematic because they are part of metabolic syndrome and usually occur together with other strong cardiovascular risk factors such as arterial hypertension, diabetes mellitus, dyslipidemia, etc. The candidate investigates asymptomatic hyperuricemia, gout without tophi and gout with tophi using complex multimodal sonography of the kidneys, heart, vessels and joints. On this topic is the dissertation "Gout and Cardiovascular Risk", the monograph "Renal and Cardiovascular Complications in Gout", as well as a number of publications with original contributions:

1. For the first time, the candidate uses a different methodological approach than the previous ones, looking for a relationship between cardiovascular risk and clinical stages of the disease and the emphasis is not placed on the level of uric acid as a risk factor.
2. For the first time, she studied the cardiovascular risk of gout with such a design, reflecting a complex approach.
3. For the first time, she performed a complex sonographic examination of patients with gout and looked for a correlation between changes in the kidneys, heart, blood vessels and joints.
4. For the first time, it establishes the degree and measures the increase in cardiovascular risk in the development of tophi.

5. For the first time, the candidate found that the development of tophi leads to changes in the vessels, mainly of the arteriosclerotic type.

6. For the first time, she found that tophi in gout is an independent, commensurate in strength and even a stronger risk factor compared to arterial hypertension. The multiple logistic regression analysis took into account all the risk factors studied and showed that the occurrence of tophi increased the risk of high resistive index of the total carotid arteries (CCARI) three times more than in arterial hypertension.

The significance of the study became clear when, at the congress of the American College of Rheumatology in November 2015, the report on the topic: *How Strong Cardiovascular Risk Factor Are Gouty Tophi?* is preceded by an interview and subsequently by the candidate's participation in a press conference together with other leading researchers in the field.

The link of gout with obesity, diabetes and psoriasis has been sought after in several studies:

Ø In this direction, the candidate investigated the influence of deposits of monosodium sodium (MNU) crystals on target organs in patients with asymptomatic hyperuricemia, patients with psoriatic arthritis and accompanying asymptomatic hyperuricemia, and patients with gouty arthritis without tophi. It found that individuals with a greater intra-articular load of MNU crystals had greater vascular rigidity and a greater load of crystals in the renal interstitium.

Ø In another study, he investigated the relationship between cardiovascular changes and MNR deposits in the joints of patients with asymptomatic hyperuricemia and no evidence of inflammatory arthritis and in patients with psoriatic arthritis and concomitant hyperuricemia. There was no difference in the distribution of cardiovascular risk factors between the groups, and no difference was found between those who undertook and did not conduct urate-lowering therapy. It is believed that in patients with asymptomatic hyperuricemia and patients with psoriatic arthritis and concomitant hyperuricemia, the mere prescription of urate-lowering therapy is insufficient to reduce the intra-articular urate load and reduce cardiovascular risk.

Publications in patients with gout in the interattack period, in which the relationship between serum concentrations of IL-1 $\beta$  and IL-18 with cardiovascular changes, as well as relationships between serum levels of reactive oxygen radicals (ROS), NO radicals and ascorbate radicals with vascular changes in the kidneys and common carotid arteries in patients with gouty arthritis without tophi and patients with subcutaneous tophi was sought. The candidate concludes that serum levels of IL-1 $\beta$  and IL-18 do not reflect the severity of gout and cardiovascular risk in the interattack period. In the level of oxidative stress, there is no difference between the earlier and late stages of the disease, but the degree of inflammation is higher in the presence of tophi. There was no association between serum concentrations of ROS products, nitric oxide radicals and ascorbate radicals with arteriosclerotic vascular changes in the kidneys and carotid arteries. In patients with gout, chronic inflammation plays a leading role in the process of atherogenesis.

An original contribution was also made to the study of morphological and immunofluorescence changes in the renal biopsy of patients with asymptomatic hyperuricemia and gout. In the percentage of damaged glomeruli as well as in the frequency of mesangial proliferation, there is no difference between asymptomatic hyperuricemia and gout. The proportion of patients with fibrosis in the interstitium > 50% was significantly higher in the gout group, but no difference was found in the distribution of patients with tubular atrophy > 50%. As in asymptomatic hyperuricemia, in gout there is a deposition of immune deposits subepithelial, subendothelial, in the mesangium and in the vascular walls. In gout, the kidneys are affected to a much greater extent. The candidate assumes that not only serum uric acid is responsible for this, but also the monosodium sodium crystals deposited in the renal interstitium, which cause a

chronic inflammatory process followed by fibrosis. It is believed that the activation of the primary immune system by soluble uric acid along with the formed crystals induces a pro-inflammatory state in the body, which activates the complement system with subsequent deposition of immune deposits in the kidneys.

The candidate evaluates the association between asymptomatic hyperuricemia and renal impairment. Asymptomatic hyperuricemia, regardless of the presence of intra-articular MNU crystals, is associated with similar renal damage. The cardiovascular risk is higher in MNU deposits in the joints.

With an original contribution are the developments related to the study of cardiorenal syndrome. For the first time in our country, the candidate conducts a study in a team through complex multimodal sonography and introduces the concept of "risky hemodynamics".

With an original contribution are also the developments that found that with the progression of chronic renal failure, changes in the vessels are primarily of the arteriosclerotic type, and not of the atherosclerotic type. Studies proving the correlations between the resistive index of the common carotid arteries and the diastolic function of the left ventricle in the different stages of gout, as well as changes in the morphology of the heart and systolic function in the presence of tophi, are also original.

A number of publications with large teams are in the field of diagnosis, immunological mechanisms, treatment and assessment of quality of life in ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's disease and others.

The candidate also describes clinical cases and rare conditions in refereed and indexed journals – retroperitoneal fibrosis, giant cell arteritis causing paralysis of the perimotor nerve, pachydermoperiostitis with antisynthetase syndrome, neurobehchet, pityriasis lichenoides chronic starting with palpable purpura after streptococcal infection, rhabdomyolysis after medication, blu-toe syndrome, nutcracker syndrome, Whipple's disease, polymyalgia rheumatica with angioedema developed in Chroniotherapy with an ACE-inhibitor, systemic sarcoidosis with perforation of the anterior nasal septum, acquired form of atypical hemolytic-uremic syndrome, rapidly progressive glomerulonephritis in granulomatosis with polyangiitis, paraneoplastic dermatomyositis from ovarian carcinoma (report).

#### **4. Educational, teaching and scientific-organizational activities**

The teaching workload of Dr. Rada Gancheva, MD, is as a full-time assistant professor of rheumatology at MU-Sofia in the period 2020-2022 and at the Department of Internal Medicine, Pharmacology and Clinical Pharmacology, Pediatrics, Epidemiology, Infectious and Skin Diseases of Sofia University "St. Kliment Ohridski" as follows:

<b>School Year</b>	<b>Hours</b>
2020/2021	268
2021/2022	258
2022/2023	117

#### **5. PhD students, postgraduate students and diploma students**

Dr. Rada Gancheva has been the head of 1 postgraduate student since 01.09.2023.

#### **6. Reviews**

Dr. Rada Gancheva is a reviewer of the journal *Rheumatology International* for 2017. (IF: 1.952).

### **7. Professional skills**

Dr. Rada Gancheva, PhD has a total work experience of 11 years and 4 months, of which as a regular assistant prof. - 2 academic years and part-time assistant prof. - 2 academic years.

Her qualities as a clinical rheumatologist are influenced by the participation and completion of many national and international courses in rheumatology. For her versatile scientific and professional realization, her knowledge of English is also of great importance.

### **8. Membership in scientific organizations**

Dr. Rada Gancheva is a member of the following national and international scientific organizations:

- § Member of the Bulgarian Society of Rheumatology
- § Member of the Bulgarian Society of Osteoporosis and Osteoarthritis
- § Member of the Gout, Hyperuricemia and Crystal-Associated Disease Network (**G-CAN**)

According to the minimum national requirements and the requirements of the Regulations on the terms and conditions for acquiring scientific degrees and occupying academic positions at the Faculty of Medicine of Sofia University "St. Kliment Ohridski" and NACID for occupying the academic position of "Associate Professor" Dr. Rada Gancheva, PhD meets more than the minimum requirements with 2033.4 points.

Based on the above data about Dr. Rada Gancheva, MD, she can be characterized as:

- o A thorough and productive researcher capable of independent scientific work in the field of internal medicine,
- o Built and competent specialist.

Documents have been submitted for the competition by two candidates - Dr. Rada Gancheva, PhD and Dr. Nonka Yurukova, PhD. Based on the materials presented, I consider Rada Gancheva, MD, PhD to be more suitable, based on the interdisciplinary scientific developments and the extremely impressive scientific production and already established international prestige.

In conclusion, I believe that Dr. Rada Gancheva, PhD meets the requirements of the Law on the Acquisition of Scientific Degrees and the Rules of Procedure for Acquiring Scientific Degrees and Occupying Academic Positions at the Faculty of Medicine of Sofia University "St. Kliment Ohridski". I propose to the esteemed scientific jury that she be awarded the academic position of "Associate Professor" in the field of higher education 7. Health and Sports, professional field 7.1. Medicine (Internal Medicine).

20.08.2024

(Prof. Borislav Georgiev, MD PhD)