

## Review

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**Subject:** competition for acquiring an academic position "Associate Professor" in the field of higher education 7. Health and sports, professional field 7.1. Medicine, specialty "Pediatrics", at the *Faculty of Medicine, Department of Pediatrics*, for the needs of the *Clinic of Pediatric Clinical Hematology and Oncology* at the University Hospital "St. Marina" - Varna, announced in State Gazette issue 17/26.02.2021. The competition was entered by one candidate - Dr. Milena Ivanova Belcheva, Ph.D.

Based on Order № P-109-17/23.04.2021 of the Rector of MU - Varna and with a decision of the Scientific Jury under Protocol № 1 of its meeting on 05.05.2021, I have been appointed to prepare a review for the academic position "Associate Professor" in the above competition.

### **I. Brief information about the competition**

All requirements and deadlines for the competition procedure have been met. Dr. Milena Belcheva is the only candidate for the position. The documents have been prepared in accordance with the requirements of Development of Academic Staff in the Republic of Bulgaria Act, the Regulation for its implementation and The Rules of the development of the academic staff of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

### **II . Brief biographical data**

Dr. Milena Belcheva was born in 1960. After graduating with honors in IV Language School "Frédéric Joliot-Curie" by studying French, she studied medicine from 1979 to 1985 graduated from the Medical University in Varna (then High Medical Institute) with excellent marks. She began working by distribution as a pediatrician in Shumen, and from 1986 to 1989 was a clinical resident in pediatrics at the Department of Pediatrics in Varna. After acquiring a specialty in pediatrics, Dr. Belcheva began working as an assistant at the Clinic of Pediatric Pulmonology at the Department of Pediatrics in Varna. From 1993 until now she has worked consecutively as an assistant, senior and chief assistant at the Clinic of Pediatric Clinical Hematology and Oncology at the University Hospital "St. Marina" and MU-Varna. From 1998 to 2000 Dr. Belcheva specializes at the Institute "Gustave Roussi" in Paris on a scholarship provided by the French government. There exam after acquiring a diploma in pediatric oncology (DUOP, 1999) at the University of Paris XI, and Postgraduate advanced specialization in pediatrics (AFSA), University of Paris V. After her return to Bulgaria, Dr.

Belcheva worked actively to establish new and modern approaches in the treatment of children's oncological diseases and formed a highly valued specialist in the national space. She acquired specialties in oncology (2004) and pediatric hematology and oncology (2006). From 2015 she is enrolled as a doctoral student at the Department of Pediatrics, Medical Varna. Meanwhile, she coordinated international project "Training of paramedics at the University Hospital" St. Marina" in partnership with the Medical University - Varna and French institutions (2007 - 2014). From 2007 to 2011 he was Secretary of the Hospital Commission for Blood Transfusion at the University Hospital "St. Marina" - Varna. Dr. Milena Belcheva has excellent language skills - fluent French and very good proficiency in English and Russian languages, and her level of knowledge of medical vocabulary is excellent. In 2020 Dr. Belcheva successfully defended her dissertation for acquiring the scientific-educational degree "Doctor" on the topic: *"Cardiovascular changes, cardiometabolic risk and bone health after successful treatment of malignant hemopathy in childhood."* The dissertation of Dr. Milena Belcheva is an in-depth, intelligent and extremely important modern study of cardiac changes, cardiometabolic risk and bone health in patients successfully treated for malignant hemopathy in childhood with great national and international contribution.

The total scientific production of Dr. Belcheva amounts to over 45 full-text publications in Bulgarian and foreign periodicals (articles and chapters in manuals/monographs), 110 participations in international and Bulgarian scientific events, with 20 abstracts published in journals (12 Bulgarian and 8 in foreign).

### **III. Teaching activity**

Educational work of Dr. Belcheva started in April 1992, when he was appointed as an assistant in pediatrics at the Medical University – Varna, initially at the the Department of Pulmonology, and soon after that to this day - to the Clinic of Pediatric Onco-Hematology of the University Hospital "St. Marina ", where she is training medical students in the 5th year, as well as residents. Over the years she has passed through all levels (senior assistant and chief assistant), and since 2015 she has been reassigned as an assistant, with the total teaching experience currently exceeding 29 years. At norm of 220 teaching hours per year, Dr. Milena Belcheva has an average annual load in the last five years, which significantly exceeds the requirements. She is fluent in French , Russian and English , and teaches both to English speaking and Bulgarian students, incl. giving lectures in the lecture course during the summer semester of each year.

### **IV. Research activity**

Dr. Milena Belcheva presents herself in this competition, she presents 10 articles referenced and indexed in world-famous databases scientific publications, equivalent to habilitation work. They carry *187.5* points, and the total number of points required by law for other scientific papers significantly exceeds the minimum requirements (see Academic Reference). In the presented list of the works of Dr. Belcheva after the dissertation defense

and not reviewed in previous competitions/defenses, a total of 40 publications are presented filed to the following criteria:

**Criterion A:** dissertation for the scientific-educational degree "Doctor"

**Criterion B (Indicator 4):** 10 full-text articles, equivalent to a monograph

**Criterion D:**

**Indicator 7:** publications and reports published in scientific journals, referenced and indexed in world databases with scientific information - **3 full-text publications and 4 published abstracts.**

**Indicator 8:** 14 full-text publications

A total of 9 publications (4 articles and 5 participations in manuals) are presented outside the minimum criteria.

Dr. Milena Belcheva is an independent author in **15.7%** and first author in **43.2%** of the submitted works, second author is in **17.6%**, and third and after third - in total **23.5%** of the works.

#### **V. Impact factor and citations:**

1. The total number of citations presented by Dr. Belcheva is **15** (210 points by Criteria D10-12) without distinction between Bulgarian and foreign resources.
2. The personal impact factor of Dr. Milena Belcheva is **18.48**. She has h-index of **2** and i-10 index of **1** according to Google Scholar.
3. Dr. Milena Belcheva has active scientific profiles in :
  - Google Scholar <https://scholar.google.com/citations?hl=bg&user=lkyCQIEAAAAJ>
  - ORCID 0000-0003-3340-7897
  - ResearchGate <https://www.researchgate.net/profile/Milena-Belcheva>
  - SCOPUS Author ID 14027963300

#### **VI. Scientific contributions of Dr. Milena Belcheva**

**The presented scientific papers and the results of the research work are thematically divided into the following areas:**

1. Late effects of treatment of childhood malignancies and follow-up of patients in long-term remission
2. Solid tumors in childhood
3. Malignant hemopathy in children
4. Emergencies and complications in the course of malignant diseases and their therapy in children

## 5. Benign hematological diseases

The contributions of the presented scientific publications of Dr. Belcheva are mainly in the field of pediatric oncology and hematology. We accept all contributions, which are arranged below by relevance and thematic direction in relation to modern legal scientometric criteria, as follows :

### ***1. Late effects of treatment of childhood malignancies and follow-up of patients in long-term remission: B 4-1; B 4-3; G 7-1, G 7-2; G 7-3, G 7-4; 3, 4, 9***

The country's first comprehensive study of children and young adults in long-term remission of acute lymphoblastic leukemia and Hodgkin's lymphoma treated in childhood was conducted. The most common and significant late effects of the therapy were evaluated, and for the first time in the country modern research methods such as Tissue Dopple Imaging (TDI) and Dual - energy X - ray absorptiometry (DEXA) were applied to this target group. The articles and scientific reports present the first in Bulgaria analysis of cardiometabolic risk, bone health and subclinical heart damage in individuals who have survived malignant hemopathy. In addition to the established excessive amount of fat mass and its redistribution by androgen type, documented in men and children treated for ALL, obesity at normal weight is emerging in more than half of the studied women with ALL (BMI, DEXA, OT).

The results of the analysis of cardiometabolic risk through integrated systems (metabolic syndrome, Framingham Risk Score) outline the early positivity of biomarkers. The long-term Framingham Risk Score (30-year risk), presented as a relative risk, is easily feasible and applicable to survivors of malignant hemopathy. Proposing this approach is valuable for clinical practice as it could guide the individual strategy for the prevention of variable cardiometabolic risk factors in patients who have experienced malignant haemopathies.

Indicative of the urgency of the problem is the rapid increase in such publications in recent years. The first study in our frequency and combination of traditional factors of cardiovascular risk in this population stands and some national characteristics . Documented a high proportion of obesity in men , treated for ALL, which corresponds to higher share zatlast firs man in the total Bulgarian population. The significant frequency of unfavorable behavioral patterns is emphasized, reflecting the tendencies in the general Bulgarian population - smoking, as well as sedentary lifestyle. An important result is the lack of physical activity in nearly one third of them, despite the lack of severe iatrogenic damage.

The applied method for simultaneous analysis of fat mass and muscle mass - and especially the inclusion in the analysis of a new and not yet applied in this target group indicator such as Z - score for individual adipose muscle mass, outlines a tendency to sarcopenic obesity in ALL survivors. It has been proven that this phenomenon is formed at an early maturity of the studied patients as a correlate of an unfavorable metabolic profile characteristic of old age.

The paper proposes categorization of the survivors of malignant hemopathy into 4 phenotypes of body composition, which has not been done in the world literature so far. This method highlights the risk group of a metabolically problematic phenotype with high

adiposity and low muscle mass (HA - LM), which is prevalent in ALL survivors, especially men. It is known that cardiometabolic risk associated with decreased muscle mass is more significant in young compared to adult persons, and but low muscle mass in combination with increased fat mass is more closely linked to insulin resistance, than the obesity itself. And Using complex analysis builds on the standard methods for assessing obesity and matches the modern concept of a common functional model of its assessment in parallel with cardiometabolic risk.

The first study in Bulgaria examining the complex bone health and bone mineral density of survivors of malignant hemopathy found a significantly reduced BMD Z-score, especially in women treated for ALL and in hypogonadal men with CL (BMD Z-score <-1 - in 13 % of ALL survivors). Women also have significantly lower BMI, body, muscle and appendicular muscle mass. In addition, they were treated with more intensive therapy and have reduced FA.

A major contribution is the correlation between anthropometric, biochemical and hormonal parameters of therapeutic exposure and behavioral patterns in the studied patients. Of particular importance is the importance of permanent and unnecessary immobilization after intensive treatment of MX in childhood, which outlines physical activity as an important tool for the prevention and delay of late morbidity.

A detailed analysis of cardiac function in survivors using modern imaging (TDI) methods revealed subclinical cardiac impairment of the systolic and diastolic function of the left and right heart chambers. This is confirmatory contribution, that emphasizes the need of early evaluation and active monitoring of patients with MH treated in childhood.

Individuals in long-term remission of ALL and malignant lymphomas were identified in Dr. Belcheva's studies as the largest group of childhood neoplasm survivors. Increasingly better and leading to longer remissions treatment requires increased attention to the late treatment effects (sequale) that occur at a young age and have a progressive course. Dr. Belcheva's works in this field, unique in the national scientific space and with a contribution to contemporary literature in general, emphasize the need for risk-oriented and lifelong medical care of survivors, that should begin during their active treatment. Creating a healthy behavioral model at the beginning of anti-tumor therapy based on specific recommendations, incl. optimization of annual reviews is the underlying string of systemic guidelines for surveillance of the patients after the end of therapy. I appreciate this contribution as an extremely important scientific and applied science aspect of Dr. Belcheva's work. Dr. Belcheva properly formulated **three basic ways** to achieve better long-term health patients: early prevention, continuity of follow-up incl. after the cure, and thereafter in specialized centers to ensure a smooth transition between childhood and adulthood - the modern concept of lifelong care.

**2. Solid tumors in childhood:** In 4-5; B 4-8, G 7-5; G 8-4, G 8-5; G 8-6; G 8-11; G 8-13; 1; 2; 5; 6; 7; 8

The main contribution in this part of the scientific developments of Dr. Belcheva is the summarization of the national experience and data related to histological, prognostic, and

therapeutic parameters in neuroblastoma, nephroblastoma, rhabdomyosarcoma, and Ewing sarcoma studied in four multicenter studies. They critically evaluate current diagnostic and treatment practices and provide guidelines for optimizing behavior in accordance with modern scientific advances. The generalized experience of the pediatric oncology centers in Bulgaria clearly demonstrates the lack of effect of therapy focused only on clinical prognostic factors in neuroblastoma, and indicates the prospect of introducing modern genetic and molecular prognostic determinants. The first Bulgarian *Guide to Neuroblastoma Behavior* sets out recommendations for risk stratification, relapse treatment, paraneoplastic syndrome behavior and follow-up of patients after the end of treatment based on evidence-based medicine - valuable and, unfortunately, not a common approach in modern medical practice in our country.

Dr. Belcheva is a recognized scientist in her guild in the field of solid tumors. Part of Scientific and articles summarize the current understanding of the biology, histogenesis, clinical manifestations, evolution, diagnosis and modern principles and methods of complex treatment of some of the most common of them (nephroblastoma, retinoblastoma, neuroblastoma). Her contemporary approach is emphasized by the attention to the multidisciplinary approach in the management of these patients.

Another part of the publications and scientific reports summarizes the own clinical experience of the Clinic of Pediatric Oncohematology in Varna, reporting their results from the treatment of both rare and typical for childhood tumors: nasopharyngeal carcinoma, retinoblastoma and nephroblastoma, incl. rare tumors and unusual primary/metastatic sites and complications.

### **3. Malignant hemopathy in childhood:** B 4-2; B 4-4; B 4-6; D 7-6

Dr. Milena Belcheva summarizes for the first time in our country the experience of the three centers of pediatric oncology hematology related to the therapeutic outcomes in children with primary AML treated with a unified AML BFM protocol, as well as for morphological variants, clinical stage, treatment, and survival in malignant non-Hodgkin's lymphomas.

Isolated reports concern other aspects of malignant hemopathy, Hodgkin's lymphoma and rare diseases. Considering the taste of the Clinic of the rare pathology, a significant contribution is the published first case in the world literature with the simultaneous presence of two different fusion transcripts: ETV 6 - RUNX 1 and BCR - ABL 1 (e1a2) in a child with B-cellular acute lymphoblastic leukemia.

### **4. Emergencies and complications in the course of malignant diseases and their therapy in children:** B 4-7; In 4-9; In 4-10; G 7-7; G 8-7; G 8-8; G 8-9; G 8-10; D 8-14

In several studies Dr. Belcheva discusses the etiology, the specific aspects of the clinical manifestation, clinical evolution and diagnostic challenges in patients with mediastinal syndrome as a life threatening condition in newly diagnosed malignant lymphomas and acute leukemias. The modern directions of resuscitation, the principles of adequate, but also minimally invasive diagnostics and the immediate control of the symptoms

in this emergency condition in pediatric oncology are summarized. Cases with critical mediastinal syndrome were documented.

Dr. Belcheva has summarized series and single cases of complications from therapy after the introduction of modern intensive protocols for the treatment of acute leukemias and malignant lymphomas. The structure of infectious complications in febrile neutropenia in the course of therapy for malignant hemopathy and solid tumors was analyzed. For the first time in the country in joint developments of the Clinic the characteristics and risk factors for tumor lysis syndrome were presented and the frequency of aseptic osteonecrosis and transient hyperglycemia in the course of antitumor therapy is analyzed. She reported a case of successful treatment with Octreotide of acute pancreatitis induced by L-Asparaginase.

#### **5. Benign hematological diseases:** D 8-1; G 8-2, G 8-3; D 8-12

With the participation of Dr. Milena Belcheva, algorithms for behavior and criteria for timely consultation with a hematologist in children with anemia and hemorrhagic syndrome have been developed, intended for doctors in the out-patient pre-hospital care.

For the first time in Bulgaria, clinical application of a protocol for induction of immune tolerance in a patient with inhibitory hemophilia has been demonstrated.

Cases of rare childhood anemia have been reported. Data from all pediatric hematology centers in the country on the incidence, clinical manifestation and behavior of Fanconi anemia in childhood were summarized and reported.

All these contributions are original and of great scientific importance.

#### **VI. Participation in scientific and training projects.**

From 2007 to 2014 Dr. Milena Belcheva is the Coordinator of the international project "Training of nurses in MHAT "St. Marina" in partnership with The Training Center "Saint Michel", to Groupe Hospitalier "Saint Augustin", Malestroit, France and the Medical University of Varna.

#### **In conclusion,**

Dr. Milena Belcheva is extremely well trained physician and lecturer in the field of paediatrics and child oncology and hematology, who devoted her entire professional contribution until this moment to the Medical University of Varna, the University Hospital "St. Marina" and to the development of the national pediatric oncology. Her dissertation filled in a large gap in the national scientific space through an in-depth and extremely significant contemporary study of cardiometabolic risk and bone health in patients successfully treated for malignant hemopathis in childhood. This study, in addition to being the only one in our country on this topic, has a great national and international contribution. The scientific works of Dr. Belcheva, which fully meet the requirements of Development of Academic Staff in the Republic of Bulgaria Act, the Regulation for its implementation and The Rules of the development of the academic staff of the Medical

University "Prof. Dr. Paraskev Stoyanov"- Varna, are a complex reflection of the work of all her colleagues in the country over the years. Many of the scientific works of Dr. Belcheva summarized and presented the achievements of Varna and Bulgarian pediatric oncology in the field of malignant hemopathies and solid tumors. The international training of Dr. Belcheva, her language skills and her exclusively conscientious and honest attitude towards patients, towards the participants in her research, to the results and their interpretation, her rich general culture and dedication in the training of students will undoubtedly be the basis for the future scientific and teaching successes of Dr. Belcheva.

All this allows me to express my positive assessment and to recommend to the Honorable Scientific jury to award Dr. Milena Ivanova Belcheva with the academic position of "Associate Professor" in the field of higher education **7. Health and sports**, professional field **7.1. Medicine**, specialty **Pediatrics** for the needs of the **Department of Pediatrics** at the **Faculty of Medicine** of the Medical University of Varna and the **Clinic of Pediatric Clinical Hematology and Oncology** at the University Hospital "St. Marina" - Varna.

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Varna



/ Prof. Dr. V. Iotova, MD /