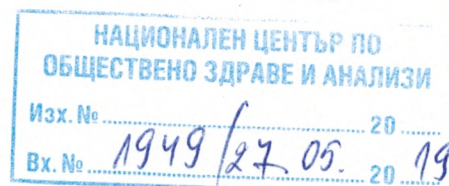


Written Opinion

from

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On the dissertation paper for obtaining Doctor's Academic and Science Degree under a PhD Program
"Social Medicine and Health Management", Higher Education Area 7. Healthcare and Sports;
Professional Area 7.1 Medicine

By **Mr. Svetoslav Valentinov Tzenov, Medical Doctor (MD)**

With topic:

MEDICAL AND SOCIAL IMPORTANCE OF FAMILIAL HYPERCHOLESTEROLEMIA IN BULGARIA

Scientific supervisors: Prof Plamen Dimitrov, MD, PhD
Assoc. Prof Evgeni Grigorov, MSc Pharm, PhD

The doctoral thesis submitted to me is an in-depth, exhaustive and comprehensive presentation of the topic of the medical and social importance of familial hypercholesterolemia in this country.

The paper consists of 155 pages and thoroughly reviews and analyses hyperlipidemia and atherosclerosis, the risk of triggering of cardiovascular disease, the contemporary treatment of hyperlipidemic patients. Other components of the conducted analysis such as the outstanding medical needs of high-risk patients, the outcomes of a study of the clinical and economic value of lowering LDL-C as well as the identification and monitoring of target patients with the help of a registry of patients with familial hypercholesterolemia in Bulgaria are presented, commented and analyzed.

The pre-defined objective and tasks of the dissertation paper are consistent with the scope of the academic specialty of the PhD program and with the content and results of the conducted studies. The methods and the materials of the research are properly selected and described, with an in-depth and well-balanced approach and are consistent with the formulated by the author contributions in terms of both theoretical and applied science.

The paper contains extensive review of the literature on the topic encompassing 191 foreign sources. The question about the absence of publications in Bulgarian is logical, having in mind the existence of Bulgarian authors and publications in English on the topic of familial hypercholesterolemia. Results of diagnostic, therapeutic, preventive, prognostic, and economic nature from studies conducted in Bulgaria and already reported to the scientific community are included in the references. The paper represents the first exhaustive scientific material on the medical and social aspects and importance of hypercholesterolemia as one of the leading risk factors for cardiovascular diseases.

The present written opinion was prepared in accordance with Art. 72, par. 1 of the Rules on the Terms and Conditions for Obtaining Science Degrees and Academic Positions with the National Center for Public Health and Analyses and in conjunction with Order No. RD-232/09.4.2019 of the Director of the latter.

The selection of the topic in my opinion is dictated also by Mr. Tzenov's personal clinical experience and interests. He demonstrates robust knowledge and expertise in the pathogenesis and contemporary guidelines and recommendations for treatment of hyperlipidemia. Large-scale epidemiological studies are presented, analyzed and commented showing that excessive cholesterol in the low-density lipoproteins (LDL-C) is a major reason for cardiovascular risk. According to further studies of familial hypercholesterolemia, the LDL-C levels are regulated primarily by cellular LDL receptors (LDLRs) and components thereof, for example proprotein convertase subtilisin/kexin type 9 (PCSK9). The identified PCSK9 gene mutations may increase or suppress the activity of LDLR and affect the overall cardiovascular (CV) risk of the individual.

In 2017-2018 together with the Society of Cardiologists in Bulgaria the creation of the first registry of patients with familial hypercholesterolemia in Bulgaria was initiated. The author of the dissertation provides a detailed account of the clinical assessment of patients as per the Dutch Lipid Clinical Network Criteria with justification of the use of the cascade screening approach in the population. At the same time, taking into account contemporary trends in identification of cardiovascular risk, data is collected that is relevant to onset of a cardiovascular incident for a given individual.

The own studies are exhaustive and properly structured. There is a balance between the background overview part and research outcomes with a of 48 pages divided in three major chapters – results from the analysis of the database in the Register of patients with familial hypercholesterolemia, study of the clinical and economic value of lowering the LDL-C and discussion of findings. The discussion of findings focuses on the significance of early diagnosis and monitoring of patients with familial hypercholesterolemia as well as on the prevention of progressing of a cardiovascular disorder. The potential benefits from the application of the Dutch Lipid Clinical Network Criteria are presented along with employing cascade screening to help improve the outcomes for this high-risk population.

The discussed economic analyses are mainly oriented towards biological therapy and they indicate that evolocumab is a highly cost-efficient medicine, the cost per life year gained for an actually treated patient being BGN 12846 and the avoidance of one cardiovascular event being achieved in the treatment of only 7 patients. Quite correctly the paper notes that the full and in-depth evaluation of the effect of administration of evolocumab is yet to be determined and that this requires at least one year of monitoring of the target patient population.

Four publications are presented in connection with the dissertation paper, including three in Bulgarian scientific periodicals and one in a foreign referenced science journal in English. The quantitative requirements of the National Center for Public Health and Analysis (NCPHA) are met, three of the publications having the author of the dissertation paper as lead author, and all being on the doctoral thesis topic.

I do endorse the obtained results and the conclusions drawn in the dissertation; they logically follow from the set objectives and tasks and substantiate the research hypothesis at hand, namely that the severe forms of dyslipidemia and hypercholesterolemia are key factors for triggering cardiovascular conditions,



early diagnosis, prevention, treatment and monitoring potentially being significant factors for improving the outlook for the high-risk population – in clinical, economic, and social terms.

Contemporary statistical analysis in processing of results was employed.

The submitted author's abstract of the doctoral dissertation meets the requirements.

Some general technical remarks can be made.

Conclusion:

The dissertation thesis submitted for discussion and evaluation is of high quality and will bring value added to the exploration of the medical, social and clinical aspects of familial hypercholesterolemia.

The dissertation paper for obtaining Doctor's Academic and Science Degree (PhD) on the part of Svetoslav Tzenov, MD, studying individually in this PhD program, meets the requirements, focuses on a specific border area, represents a novelty for Bulgaria and has significant advantages in view of introduction of new policies, changes in medical practice and decision-making at governance level.

Upon reviewing in details the package of materials submitted for the dissertation of Dr. Tzenov, my opinion is that the topic, the volume, the findings, the conclusions and the formulated contributions are fully consistent with the Rules of the NCPHA, the PhD program, and are a result of own research and studies of the author.

In view of the foregoing arguments and the submitted dissertation thesis, **I confidently give my positive evaluation** and propose to the Honorable Members of the Scientific Jury to confer with **Doctor's Academic and Science Degree (PhD)** Mr. Svetoslav Valentinov Tzenov, MD for the conducted study presented as dissertation work, author's abstract of doctoral dissertation, results achieved, publications made and contributions.

Sofia,

23.5.2019

Signature:

