TO

THE CHAIRMAN OF THE SCIENTIFIC JURY,

DETERMINED BY ORDER No. 15-05-78/19.03.2025.

THE EXECUTIVE DIRECTOR AND THE PROCURATOR

TO "ASC UMBAL TOKUDA" FED

Per your Minute No. 1,

I submit attached:

REVIEW

From prof. Maria Toncheva Staevska - Kotasheva, MD

Department of Allergology, Medical University - Sofia Specialty - Internal Medicine, Clinical Allergology External member

Dissertation for the award of doctoral degree

Field of higher : 7 "Health and sport"

Professional field: 7. 1 "Medicine"

Ph.D. programme: 'Dermatology and Venereology'

Author: dr Zdravko Dobrev Dimitrov

Specialist in pediatric diseases and clinical allergology

ASC Tokuda University Hospital - Sofia, Clinic of Skin and Venereal Diseases

Subject: DIAGNOSTIC VALUE OF SPECIFIC ALLERGY TESTS IN DETERMINING TOLERANCE TO COW'S MILK IN PATIENTS WITH APCM

Scientific supervisor: Prof. Dr. Nikolay Konstantinov Tsankov, MD

Form of the PhD: independent training

This review is based on a complete review of the dissertation, the abstract, the publications on the topic and the relevant regulatory documents for the award of the PhD.

I declare that I have no publications in common with the PhD student, except for one publication in 2014, which is not related to the topic of the dissertation.

Presentation of the PhD student

Biographical data

Dr. Zlatko Dobrev Dimitrov was born on 1. 06. 1977 in the town of. He was born in 1977 in Nebit - Dag, Turkmenistan.

Graduated in medicine at the University of Thrace - gr. She graduated from Stara Zagora University in 2003, after which she started working at the hospital in Galabovo. From 2005 to 2010 he was an assistant at the Children's Clinic of the of Thrakia University and acquired a specialty in "Pediatrics" in 2010. Then he started specialization in Clinical Allergology at the Clinic of Allergology of the University Hospital of Alexandrovska and acquired a specialty in "Clinical Allergology" in 2014. Since 2011 she has been working in the ASC of Tokuda University Hospital - Sofia.

PhD student is of independent preparation with topic of thesis dissertation "Diagnostic value of specific allergy testing in patients with APCM".

She is fluent in written and spoken English and Russian.

He has participated in international and national scientific forums.

She is a member of the Bulgarian Society of Allergology, the Bulgarian Paediatric Association and the European Society of Immunology and Clinical Immunology (EAACI).

I. Relevance of the topic

The dissertation topic is extremely timely and practically relevant, fitting in the context of the increasing incidence of allergic diseases in childhood, with a particular focus on food allergies. Allergy to cow's milk proteins (ACMP) occupies a central position among food allergies in infancy and poses a major challenge for diagnosis, treatment and follow-up. The development of more accurate, safer and affordable diagnostic methods is a priority in modern clinical allergology. In this context, Dr. Dimitrov's dissertation addresses a current deficit in scientific and clinical practice by focusing on assessing the diagnostic value of SPT, APT, sIgE, and OFC tests in children with APCM and developing an algorithm to predict tolerance.

II. Structure and content of the dissertation

The dissertation is built on 146 pages of main text, 21 figures and 29 tables. The author presents a coherent introduction, literature review, aims and objectives, methodology, results, discussion, conclusions, contributions and bibliography. The bibliography includes 307 sources, of which 303 are in English, mainly from the last decade. The abstract (46 pages) correctly reflects the content of the thesis. publications and participation in a scientific forum are presented, which meets the regulatory requirements. The literature review is thorough and analytical, covering pathogenesis, clinical presentation, diagnostic methods and therapeutic options in APCM, as well as a critical review of tests of low diagnostic value - demonstrating an excellent knowledge of the subject matter.

III. Aim, objectives, methodology

The aim is clearly stated - to establish the prognostic value of various allergy tests for the assessment of tolerance to cow's milk. Eight tasks covering epidemiology, diagnostics and statistical modelling are formulated. A total of 248 children (3 months - 9 years) were studied and divided into subgroups assessed by SPT, APT, sIgE and OFC. Data were processed with SPSS (v13), descriptive statistics, z-tests, logistic regression and Clopper-Pearson analysis were used. An algorithm and clinical practice guidelines were developed. The methodological approach was adequate, with sufficient sampling and precision of the applied diagnostic criteria and statistical tools.

IV. Main results and discussion

The results showed that the most common manifestations of APCM in the study population were maculopapular rash, urticaria, atopic dermatitis and angioedema. Evaluation of the diagnostic value of each test individually and in combination against OFC as the gold standard showed that the combined approach resulted in higher sensitivity and specificity. A logistic model was created to predict tolerance that incorporated clinical and laboratory parameters. The author reasonably discusses the results against current international data, demonstrating analytical capacity and critical thinking. A practically applicable diagnostic algorithm is formulated that represents a valuable contribution to clinical practice.

V. Scientific contributions

Among the most significant contributions are:

1. First study of its kind in Bulgaria with simultaneous assessment of SPT, APT and sIgE in APCM;
2. Introduction of APT as an element of the diagnostic algorithm in food allergies;
3. Development of a logistic regression model with predictive value for cow milk tolerance;

4. Development of an algorithm applicable to the daily practice of the clinical allergist;
5. Confirmation of the importance of a combined diagnostic approach compared to isolated methods;
6. For the first time, the frequency of reactions in children under and over 24 months of age was assessed in both girls and boys i.e. a detailed characterization of clinical phenotypes of APCM in the Bulgarian pediatric population.

VI. Publications related to the thesis

Publications and scientific events related to the dissertation are also presented.

In connection with the dissertation, 3 articles and one participation in a scientific forum on the topic of the dissertation were presented. In terms of number and quality, the scientific works meet the minimum requirements for the PhD according to the "Law on Development of Academic Staff in the Republic of Bulgaria, its Implementing Regulations and the Regulations of the ASC of the Tokuda University Hospital - Sofia. Since not all data are published, it is recommended that the PhD student makes an effort to publish in English, which will make the results of his work available for analysis and citations by the international allergology community.

VII. Abstract

The abstract covers 46 pages and corresponds to the materials included in the thesis. The abstract reflects the content of the thesis and meets the requirements.

VIII. Critical comments and recommendations

The dissertation is grounded, logically structured and scientifically sound. However, in the spirit of academic rigor, several possible areas for improvement should be noted, which do not diminish the essentially high scientific and applied value of the work:

1. The literature review is too extensive is not very directly related to the problem developed in the thesis. In fact, one part of the literature review is located located in methods and results - it is appropriate to move these pages to the first part. There is no final summary to critically link the sources presented to the stated purpose of the study. Its addition would have strengthened the logical integrity.

2. It is possible to structure the results even more clearly by dividing the statistics by age and clinical subgroups, which would facilitate interpretation. In fact instead of the dichotomous division positive/negative specific IgE and SPT, which show no correlation with OFC, it may be better to look for a quantitative estimate and find a value that has a good PPV, as found in most studies and hence the recommendations for the use of these tests.

3. The author has used a scholarly style, but repetition and long sentences occur here and there, which could be optimized for future publication. The translation of some terms used in the scientific literature is inaccurate e.g. challenge instead of provocation sample, which is used in Bulgarian language and other similar inaccuracies that hinder a more accurate perception of the text

4. It would be good to have a discussion related to the results obtained and how they compare with the literature. There are specific suggestions for implementation of the diagnostic algorithm developed in clinical paediatric practice that does not follow from the results (they do not correlate with the recommendations found).

The above remarks are constructive in nature and are intended to contribute to the further refinement of the work without detracting from its merits.

It is important to note that OFCs are very underrepresented in pediatric allergy practice in our country, which is a big problem. The practice at Tokuda Hospital is one of the few places in Bulgaria where this is done thanks to Dr. Zlatko Dimitrov. For this and for the introduction of APT also for the first time in our country the PhD student should be congratulated. The opportunity to do OFC, which is the "gold standard" in the diagnosis of APCM, also allows him to critically examine the value of other diagnostic methods in this difficult area at small children.

IX. Conclusion

The dissertation work of Dr. Zlatko Dobrev Dimitrov represents a complete, independent, original scientific research with a high degree of theoretical depth and applied orientation. The topic is topical, the contributions - significant, and the presentation - scientifically and methodologically sound. The author demonstrates in-depth knowledge in the field of clinical allergology, an analytical approach to the interpretation of results, and the ability to independently research work.

As a scientific reviewer I give a positive evaluation of the dissertation and I propose the esteemed scientific jury to award to Dr. Zlatko Dobrev Dimitrov the educational and scientific degree "Doctor" in the scientific specialty "Dermatology and Venereology", professional field "Medicine".

30 Apr 2025

Sofia

Signature:

Prof. Maria Toncheva Staevska - Kotasheva, MD, Ph.D