## **OPINION**

#### from

# Prof. Dr. Valeria Ignatova Kaleva, PhD

Of dissertation work for awarding the educational and scientific degree "Doctor" in the Field of Higher Education 4. Natural studies, mathematics, and informatics, Professional direction 4.3 Biological sciences", Scientific specialty "Genetics

Author: Dr. Dinnar Ali Yahya

# *Topic:* Analysis of molecular-genetic markers in patients with acute myelogenous leukemia

Form of doctoral studies: full-time

Department: Medical Genetics, MU-Varna

Research supervisors: Prof. Dr. Ilina Dimitrova Micheva, PhD,

Assoc. Prof. Dr. Trifon Georgiev Chervenkov, PhD,

# General presentation of the procedure

By order No. R-109-82 dated 21.03.2024 of Prof. Dr. Dimitar Raykov, MD, Rector of the Medical University - Varna, based on the decision of the Faculty Council of the Faculty of Medicine (Protocol No. 18/11.03. 2024) I have been selected as an internal member of the Scientific Jury evaluating the dissertation work of Dr. Dinnar Ali Yahya on the topic "Analysis of molecular genetic markers in patients with acute myelogenous leukemia". According to the decision of the first meeting of the scientific jury, I am appointed to prepare an opinion.

The presented set of materials for the procedure for awarding the educational and scientific degree "Doctor" is complete, available in electronic and paper formats, and follows the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Rules for the Development of the Academic Staff of the MU-Varna.

#### Short biographical information about the PhD student

Dr. Dinnar Ali Yahya graduated from secondary education in 2011 at the "Alexander Pushkin" PE in Varna, and in 2017 - higher education in medicine at the "Prof. Dr. Paraskev Stoyanov", Varna. In 2019, she was enrolled as an assistant in the Department of Medical Genetics at the same university and as a specialist in "medical genetics" in the Medical Genetics Laboratory sector at UMBAL "St. Marina", Varna. In 2023, she acquired a "medical genetics" specialty. In 2020, she was enrolled as a full-time doctoral student by order of the Rector of the MU - Varna No. R-109-475/04.11.2020 with a dissertation topic: "Analysis of molecular genetic markers in patients with acute myelogenous leukemia". She was dismissed with the right of

defense by the decision of the Faculty Counsil and order of the rector of the MU - Varna No. R-109-82/21.03.2024.

Dr. Yahya's academic interests are in the fields of cytogenetics, oncocytogenetics, and molecular oncogenetics, maintaining and developing through participation in courses, conferences, and scientific forums in the country and abroad. She has participated in one university and two international projects.

She is a member of the Bulgarian Society of Human Genetics and Genomics, the Bulgarian Scientific Society of Hematology, the European Society of Human Genetics (ESHG), the European Cytogeneticists Association (ECA) and the International Society for Prenatal Diagnosis (ISPD). She speaks English, Russian, Turkish, and Italian languages.

## **Relevance of the topic of the dissertation**

Acute myeloid leukemia (AML) is a hematological malignancy, the diagnosis of which is based on specific genetic characteristics. While conventional cytogenetic analysis (CCA) continues to be the "backbone" of AML classification, in recent years the evaluation of certain gene mutations has become the standard for diagnosis, prognostic stratification, and personalization of therapeutic strategies. Genomic technologies rapidly increase the understanding of the molecular pathogenesis of AML, and this new information is being actively evaluated in various mutational panels aiming at achieving precise diagnosis and further improving treatment outcomes.

In this sense, I find the topic chosen by the dissertation researcher for the study of new molecular genetic methods for the diagnosis of AML to be extremely relevant, suitable for the development of dissertation work, and useful in a scientific and applied sense.

#### General characteristics and structure of the dissertation work

The presented dissertation contains 130 standard pages and is illustrated with 12 tables and 15 figures. It is structured according to generally accepted requirements including content, abbreviations, introduction, literature review, aim and objectives, contingent and methods, results, discussion, conclusion and prospects for future work, conclusions, contributions, list of scientific publications, and participation on the topic of the dissertation, a bibliographic reference including 201 literary sources, of which 5 in Cyrillic and 196 in Latin, and appendices.

# Literature review

The literature review is comprehensive and demonstrates excellent knowledge of the problem. It is structured in three sections detailing the genetic characterization and classifications of AML, ELN risk stratification, and the most used molecular genetic markers and methods.

A large part of the third section is devoted to the molecular genetic methods currently used in the modern diagnostic approach in some hematological neoplasias: CCA, FISH, SNR-microarray, fusion gene sequencing panels, and NGS/MPS. For each of them, the individual advantages and limitations are indicated and the real possibilities for their application in routine clinical practice are discussed. Special attention is paid to the relatively new MLPA (Multiplex Ligase-dependent Probe Amplification) method, for which there is still insufficient data confirming its diagnostic value in patients with oncohematological diseases.

Analyzing the role of molecular genetic analyses in the initial assessment of patients with newly diagnosed AML, at the end of the literature review, the dissertation summarizes the current literature data and international recommendations. A conclusion is formulated according to which accurate diagnosis, risk stratification and prognosis correlate with a combination of at least two genetic methods: initial CCA and molecular genetic to detect changes in the genome.

The *Objective* is formulated synthetically: To assess the applicability of the MLPA method for reporting AML-specific molecular-genetic markers in the routine clinical-diagnostic activity for the evaluation of patients with newly diagnosed AML.

The implementation *Tasks* follow the logic of the literature review and their solutions are in sync with the diagnostic methods used.

The *Patients and Methods* section is presented on 7 pages. The study is prospective and was conducted in the Laboratory of Medical Genetics at UMBAL "St. Marina" - Varna. It included 61 adult patients with newly diagnosed AML and 21 healthy individuals. The research design and methods are appropriately chosen and described in detail and clearly. The work was carried out according to the rules of good scientific practice with the permission of the Committee on Ethics of Scientific Research at the Medical University - Varna. Statistical methods and software programs for data processing are presented.

The presentation of the *Results* is spread over 14 pages and includes two subsections. The sequence of the set tasks was observed and the concept of the scientific development was followed. The results are scientifically sound, practically applicable, and relevant for use in future research. The competence of the dissertation student and his interpretive qualities are explained.

The discussion of the results is presented in a separate section *Discussion*, which is developed over 22 pages and follows the logic of the conducted study. It presents an assessment of scientific results, compared with data from modern literature. Discussions are presented in concise and literary language, demonstrating competence and analytical thinking.

*The conclusions* of the dissertation work are 6 and are formulated as an extract of the results of the five assigned tasks.

The work ends with a presentation of **7** *Contributions*, the merit of which lies in their originality in a scientific and applied aspect.

## Evaluation of the dissertation work-related publications

The dissertation student presents 3 full-text publications, two in foreign periodicals. In all of them, Dr. Dinnar Yahya is the first author, which is a testament to her contribution to the development of the scientific concept, data collection, study design, summary of results, and publication. Also presented are 4 published abstracts from participation in scientific forums, where the dissertation student is the first author.

## Abstract

The abstract is over 52 pages and structured similarly to the dissertation work. It summarizes the purpose and tasks, the achieved results, the discussion, the conclusions, and the self-evaluation of the contributions. The exposition is illustrated with 5 tables and 11 figures.

## **Critical remarks**

There is no basis for relevant critical remarks.

# Conclusion

In terms of structure, volume, and content, the presented dissertation meets all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of the LDASRB and the relevant Regulations of the Ministry of Education - Varna. It is an original development of the dissertation student, demonstrating theoretical training, professional skills, and the ability to conduct scientific research.

Given the above analysis, I give a positive assessment of the dissertation work "Analysis of molecular genetic markers in patients with acute myelogenous leukemia" and propose to the respected Scientific Jury to award Dr. Dinnar Yahya the educational and scientific degree "Doctor" in the scientific specialty "Medical Genetics".



Date: 20.05.2024

Prepared the statement: .....

(Prof. Dr. Valeria Kaleva, PhD)