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Application of mathematical models in predicting drug dosage and its efficacy

Mohamed Chahine[1], Nikolaos Tzenios[2], Ksenia V. Zavidovskaya[1], Lyudmila P. Lazurina[1] ✉, Yulia M. Dotsenko

[1] Kursk State Medical University of the Ministry of Health of the Russian Federation
3 Karl Marx Str., Kursk 305041, Russian Federation

[2] Charisma University, Grace Bay, Turks and Caicos Islands

✉ e-mail: lazurinalp@kursksmu.net

Abstract

The purpose of the research *is to form a comprehensive understanding of how mathematical models are used to interpret complex dynamics related to the distribution, metabolism and excretion of drugs in the human body. The use of mathematical models to predict the required dose of drug prescriptions and establish its effectiveness means a paradigm shift in the field of pharmacology.*

Methods. *The methodology used in this study was aimed at identifying and analytically reviewing articles that correspond to the objectives of the study. The publications included in the analysis were analyzed and data extracted, focusing on key information such as the mathematical modeling methodology used, the exact predicted treatment effects, the populations studied, long-term prognostic effects, and the assessment of the use of various drug dosing regimens.*

Results. *In total, 12 publications were analyzed, which used four different methodologies: models with the effects of several different conditions, models that take into account the occurrence of various discrete events, models based on the effects of informative signs taking into account the physiology of individuals, as well as survival models and generalized linear models.*

Conclusion. *The conducted study of the current state of mathematical modeling in medical research for the purpose of comparative effectiveness is intended for practicing scientists and doctors in conducting further research and introducing innovations. Despite the challenges, the potential impact of these models aimed at bridging the gap between the controlled clinical environment and the real health context is undeniable. The use of mathematical modeling methods to predict the dosage of medicines will improve the quality and effectiveness of personalized medical appointments in the coming years.*

Keywords: *mathematical modeling; forecasting; efficacy; drug.*

Conflict of interest: *The Authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.*

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Применение математических моделей для прогнозирования дозировки лекарств и их эффективности

Шехине Мохамад Туфик[1], Тзениос Николаос[2], К. В. Завидовская[1], Л. П. Лазурина[1] ✉, Ю. М. Доценко[1]

[1] Курский государственный медицинский университет Министерства здравоохранения Российской Федерации ул. К. Маркса, д. 3, г. Курск 305041, Российская Федерация

[2] Университет Харизмы, Грейс-Бей, острова Теркс и Кайкос

✉ e-mail: lazurinalp@kursksmu.net

Резюме

Цель работы *заключается в формировании всестороннего понимания того, как математические модели применяются для интерпретации сложной динамики, связанной с распределением, метаболизмом и выведением лекарств в организме человека. Использование математических моделей для прогнозирования необходимой дозы назначений лекарственных препаратов и установления его эффективности означает изменение парадигмы в области фармакологии.*

Методы*, использованные в данном исследовании, были направлены на выявление и аналитический обзор статей, соответствующих целям исследования. Публикации, включенные в анализ, были подвергнуты анализу и извлечению данных, сосредоточив внимание на ключевой информации, такой как используемая методология математического моделирования, точные прогнозируемые эффекты лечения, изучаемые популяции, долгосрочные прогностические эффекты и оценка применения различных режимов дозирования препаратов.*

Результаты*. Всего было проанализировано 12 публикаций, в которых использовались четыре различные методологии: модели с воздействием нескольких различных состояний; модели, учитывающие возникновение разнообразных дискретных событий; модели, основанные на воздействии информативных признаков с учетом физиологии индивидов, а также модели выживания и обобщенные линейные модели.*

Заключение*. Проведенное исследование текущего состояния математического моделирования в медицинских исследованиях с целью сравнительной эффективности предназначено для практикующих научных работников и врачей при проведении дальнейших исследований и внедрении инноваций. Несмотря на существование проблем, потенциальное влияние этих моделей направлено на преодоление разрыва между контролируемой клинической средой и реальным контекстом здравоохранения неоспоримо. Применение математических методов моделирования для прогнозирования дозировки лекарственных средств позволит повысить качество и эффективность персонифицированных медицинских назначений в ближайшие годы.*

Ключевые слова: *математическое моделирование; прогнозирование; эффективность; лекарственные назначения.*

Конфликт интересов*: Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.*

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Introduction

Within the dynamic realm of pharmaceutical research and clinical practise, the optimisation of drug dosages emerges as a crucial and central obstacle. The advancement of novel methodologies that reconcile

scientific knowledge with patient well-being has been motivated by the objective of optimising therapeutic effectiveness while mitigating potential negative outcomes. The core of this revolutionary approach is centred around the utilisation of mathematical models, which has brought about a significant change in our comprehension of pharmacokinetics, pharmacodynamics, and the personalised reaction to medication treatment.

For decades, pharmacologists, doctors, and researchers have been captivated by the complex interplay between drug dosage and efficacy. The persistent problem has prompted the emergence of mathematical models as a potent tool that not only enriches our understanding of drug behaviour within the human body but also facilitates accurate forecasts of optimal dosages customised for specific patients.

This paper undertakes a thorough investigation of the "Utilisation of mathematical models for the purpose of predicting drug dosage and evaluating its effectiveness". As we navigate the complex terrain of mathematical modelling in the realm of medication dosage prediction, it becomes evident that the integration of computational methodologies and pharmaceutical sciences is not just a choice, but a need in our quest for enhanced safety and efficacy in pharmacological treatments.

A mathematical model functions as an outline for comprehending and simulating natural occurrences or intricate systems [1]. The utilisation of these models is of great significance as they serve as indispensable instruments for acquiring insights and knowledge pertaining to the system they depict. Mathematical models are of great significance in the field of drug development.

Physiology-based models provide a comprehensive comprehension of the biological mechanisms involved, aiding researchers in establishing appropriate initial dosages for experimental pharmaceuticals [2].

Pharmacokinetic and pharmacodynamic models take into account the processes of drug absorption, distribution, metabolism, and elimination inside the body, as well as the impact of these medications on physiological systems. With the assistance of these individuals, researchers are able to optimise the dosages utilised in subsequent investigations, so guaranteeing the appropriate quantity of the medication is administered to achieve optimal therapeutic efficacy while minimising any adverse reactions. The disparity between the results obtained from randomised controlled trials (RCTs) and the actual impact observed in real-world situations has been referred to as the "efficacy-effectiveness gap" [3]. Various strategies have been proposed to address this disparity and to forecast the practical efficacy of randomised controlled trials (RCTs) based on evidence synthesis models. Mathematical models have the capacity to simulate the progression of a disease for either an individual or a cohort of patients, considering different interventions and conditions.

This work aims to provide a comprehensive understanding of how mathematical constructs facilitate the interpretation of complex dynamics associated with drug distribution, metabolism, and elimination in the human body. This application facilitates a dynamic collaboration between the disciplines of mathematics and medicine, the integration of data and decision-making processes, and the convergence of scientific advancements with patient care. The utilisation of these models and the effective

management of pharmacological therapy in an ever-changing landscape is a shared obligation, necessitating precision, empathy, and a steadfast dedication to the welfare of the individuals under our care.

Materials and methods

The methodology employed in this research focused on identifying and selecting articles that meet specific criteria aligned with the research objectives.

Articles were considered eligible if they applied any mathematical modeling approach to make predictions concerning treatment effects. The anticipated purpose of these models was to offer valuable insights into dimensions that were not explicitly examined in the current Randomised Controlled Trials (RCTs). The scope of predictions encompassed articles that provided prognostications regarding the impact of treatments on variables that extended beyond those specifically investigated in previous randomised controlled trials (RCTs). This entailed prognostications pertaining to diverse demographics, diverse healthcare environments, enduring consequences, or diverse administration schedules.

Articles that failed to explicitly discuss the shift from treatment efficacy, as assessed in controlled clinical trial environments, to the real-world application of treatment effectiveness were not included in the analysis. This criterion ensured that the selected research were focused on bridging the gap between controlled clinical environments and real healthcare contexts.

In order to ascertain pertinent publications, an exhaustive review of the literature was undertaken across many scholarly databases, including PubMed, Web of Science, Scopus, and pertinent medical journals, among others. The search technique comprised a combination of keywords and controlled language topics linked to mathematical modeling, therapeutic effects, prediction, populations, locations, long-term results, and dosing regimens. The utilisation of Boolean operators, specifically AND and OR, was employed in order to enhance the precision of the search queries and guarantee their relevancy.

Articles that did not satisfy the inclusion criteria or were clearly excluded were omitted. The remaining items were subjected to a comprehensive examination of their complete texts.

The publications included in the analysis were subjected to data extraction, focusing on key information such as the mathematical modelling methodology employed, the precise treatment effects projected, the populations or locations being studied, the long-term results investigated, and the various dosage regimens evaluated.

A quality assessment was conducted on each chosen article to assess the rigour and validity of the mathematical modelling approach and the methodology used to address the gap between efficacy and effectiveness. The objective of this study was to ascertain the dependability of the predictions generated by the modelling process.

Results and their discussion

Four articles employed multi-state models. The models under consideration are characterised as time-dependent stochastic processes, wherein a discrete collection of potential outcomes, sometimes referred to as states, are defined. The model provides an explanation of the probability associated with transitioning from one condition to another. A distinction is made between population-level and individual-level multi-state models. The latter are

alternatively referred to as microsimulation models (MSMs) [4]. Both population-level models and Microsimulation Models (MSMs) frequently exhibit a characteristic known as the Markov property. This property implies that the transition probabilities between different states are considered to be independent of the past, given the current state. In the realm of population health research, Markov cohort models, also known as population-level multi-state Markov models, are widely utilized for analytical purposes.

Population-level multi-state models offer a robust framework for examining the transitions between various health states within a given population. These models provide insight into the enduring effects of medication therapies, enabling a thorough assessment of the influence of dose approaches on overall health results. Briggs and Sculpher assert that population level multi-state models are highly appropriate for the purpose of simulating the progression of chronic diseases [5]. The patient's clinical condition or health status is characterised by many states. The states are considered to be mutually exclusive, indicating that it is not possible for a patient to simultaneously exist in many states. There are two types of models: discrete models and continuous-time models.

In discrete-time models, transitions occur exclusively at specific time intervals. The temporal duration between consecutive time points can be referred to as a cycle, while the likelihood of transitioning from one state to another during a single cycle is denoted as the transition probability. In a theoretical framework consisting of a set of n states, the whole set of potential transition probabilities can be represented and organised in a transition matrix with dimensions (n × n). Certain transitions may be prohibited, resulting in a zero value in the matrix. This reduces the number of probabilities that need to be evaluated. For instance, individuals in a deceased state are unable to undergo more transitions.

Microsimulation models (MSM) are utilised to replicate the life paths of individual patients, encompassing the complexities inherent in their distinct experiences within the healthcare system. The use of mathematical simulation models (MSMs) has been employed in the examination of health policy inquiries pertaining to many medical conditions, including cancer screening and the management of diabetes, cardiovascular disease, stroke, osteoporosis, and liver disease [6]. Multistate models (MSMs) can be classified into two categories: discrete-time models and continuous-time models.

We have identified two articles through the utilisation of mainstream media (MSM). In their study, Smolen et al. made predictions regarding the likelihood of stroke within a span of five years for a cohort of individuals diagnosed with asymptomatic carotid artery stenosis. The researchers employed a simulation approach using discrete states to estimate the occurrence and timing of patient mortality or stroke events. To establish the accuracy of the model, the authors conducted a comparison between the model's predictions and the observed stroke-free survival rates and stroke occurrences in a population that was similar in nature.

Discrete event simulation models provide a detailed viewpoint on patient experiences by simulating healthcare events as distinct entities. Through this action, they offer significant contributions to the understanding of clinical workflow dynamics and

the impact of various dosage regimens on patient trajectories. The utilisation of discrete event simulation enables the integration of discrete and continuous outcomes [7]. Examples of events may include strokes, fluctuations in blood pressure, emergence of new lesions on magnetic resonance imaging, or advancement on the extended disability status scale. The Markov property may or may not be present in DES models. The DES models offer a structured approach for conducting stochastic simulations at the individual level.

The utilisation of discrete event simulation models has been a prevalent practise in the field of operations research for an extended period of time, as highlighted by Guo et al. [8] This approach is particularly valuable in addressing the challenge of resource allocation within a context of limited availability.

Physiology-based models extensively explore the molecular foundations of drug behavior within the human body. These models take into account physiological processes, drug distribution specific to organs, and complex pharmacokinetic-pharmacodynamic connections in order to forecast drug concentrations at the cellular and tissue levels. Physiology-based models enable the ongoing modelling of disease-relevant systems in a human person over time. The Archimedes Model, as described by Schlessinger and Eddy, is an illustrative instance of a physiology-based model that employs algebraic and ordinary differential equations to depict fundamental elements of human physiology, disease, and the reaction to medical interventions [9]. Continuous functions are used to explain the biological variables and their interactions, allowing for varying values at different points in time, as opposed to a fixed number of states or discrete occurrences [10]. The biomarker values of each patient, such as blood pressure, cholesterol, bone mineral density, patency of coronary arteries, contractility of the myocardium, and cardiac output, have the potential to vary over time. The selection of the model design is determined by the biological characteristics of the disease, the mechanism via which the intervention operates, and the data that is accessible.

At present, Archimedes encompasses a range of indications including coronary artery disease, diabetes and its associated consequences, congestive heart failure, stroke, and hypertension [11]. One potential use of this approach is the evaluation of various therapies, guidelines, or disease management programmes. By including comorbidities, it becomes possible to make predictions about long-term results or outcomes within distinct populations. The process of validation was conducted by juxtaposing the results of the model with the data derived from significant clinical studies [12].

In the study conducted by Schuetz et al., the Archimedes Model was employed to forecast the potential outcomes of varying dosages and types of statins (namely, rosuvastatin 20 mg vs. atorvastatin 40 mg and rosuvastatin 40 mg vs. atorvastatin 80 mg) in terms of the occurrence of initial major cardiovascular events among individuals diagnosed with diabetes [13].

Survival models and generalized linear models are statistical methodologies that offer frameworks for the analysis of time-to-event data and the examination of the association between variables and pharmacological responses. These findings provide a strong basis for comprehending the influence of various dosages on the outcomes of survival and other related measures.

The utilisation of predictive models that extend beyond the limited follow-up period provided by randomised controlled trials (RCTs) is valuable in informing decisions pertaining to pharmaceuticals and other medical procedures [14]. Survival analysis employs several methodologies, including nonparametric methods such as the Kaplan-Meier estimator, semi-parametric methods like Cox regression, and parametric methods based on survival distributions such as the exponential, Weibull, Gompertz, and others.

Two research were identified that utilised survival models in order to forecast the relative effectiveness. In their study, Clarke et al. utilised simulations grounded in multiple survival models to predict the prevalence of significant complications and mortality associated with diabetes [15]. The interventions consisted of two different regimens for controlling blood glucose levels: intense and conventional. The outcomes of patients who were randomly assigned to either conventional or intensive blood glucose control in the UKPDS study [16] were predicted by the model over their lives. In their study, Clarke et al. employed proportional hazards Weibull regression to analyse the occurrence of diabetes-related complications [17]. Additionally, logistic and Gompertz regression models were utilised to examine diabetes-related mortality. The researchers conducted a comparison between the projected cumulative occurrence of various complications and mortality rates with the actual cumulative occurrence. This was accomplished by employing non-parametric (life table) methodologies for calculation.

The conventional assumption in linear models is that the dependent variable is characterised by continuity and follows a normal distribution. Generalised linear models (GLMs) are an extension of linear models that allow for the analysis of data with response variables that do not follow a normal distribution. The listed research employ extrapolation techniques to predict outcomes over extended timeframes beyond the scope of the randomised controlled trials (RCTs) under consideration.

In their study, Hughes and Dubois employed a Generalised Linear Model (GLM) to make predictions on the efficacy and expenses associated with various therapies for overactive bladder and urge urine incontinence, taking into account the temporal dimension [18]. The study involved a comparison of oxybutynin extended-release and tolterodine extended-release, as well as tolterodine immediate-release, oxybutynin immediate-release, and placebo. The estimation of the frequency of incontinent episodes per week was conducted using a negative binomial distribution function. This estimation was based on individual patient data obtained from many randomised controlled trials, with a median treatment length of 4-5 weeks. The estimated frequency was then extrapolated to represent a one-year period. The data pertaining to adverse events was obtained from randomised controlled trials (RCTs). Multiple sensitivity assessments were conducted. In order to assess internal validation, the projected values were compared to the observed data. No external validation was conducted.

The application of mathematical models in the prediction of drug dose and effectiveness is a continuously expanding and dynamic area of study that holds the potential to revolutionise the processes of drug development, testing, and administration. Within this discourse area, we shall explore the fundamental discoveries, ramifications,

and obstacles that emerge from the use of diverse mathematical models in the field of pharmacology and personalised medicine.

Mathematical models, including physiology-based models and pharmacokinetic-pharmacodynamic models, are of great significance in optimising the process of drug development. These models enable researchers to make decisions based on data throughout all stages of the research process, ranging from preclinical investigations to clinical trials. Through the utilisation of these models, the pharmaceutical sector has the capacity to mitigate the expensive and time-intensive elements associated with drug development, leading to enhanced operational efficiency and potentially expedited availability of groundbreaking therapeutic interventions.

One of the most notable advantages of mathematical modelling is in its potential to make significant contributions to the field of personalised medicine. Through the incorporation of patient-specific data encompassing genetics, demographics, and clinical characteristics, these models facilitate the customization of drug dosages and treatment regimens to suit the unique needs of individual patients. This technique not only improves the effectiveness of therapy but also reduces the occurrence of negative side effects, so promoting the emergence of a new age in precision medicine. With the accumulation of further patient data and the advancement of modelling approaches, it is foreseeable that there will be an enhanced level of customization in medication therapy.

Each of the research presented in the analysis exhibited certain limitations. One of the primary limitations lies in the absence of validation regarding the prediction performance of the utilised models. Among the models examined, a mere three models conducted external validation by employing data distinct from that which was utilised throughout the model's development. The availability or accessibility of appropriate data for external assessment may have been limited or challenging. However, it is important to note that the absence of external validation is a significant constraint, as highlighted by Altman et al. [19] Decisions must not to be predicated upon forecasts derived from inadequately verified models.

Another constraint pertains to the Markov assumption. A significant number of the models were dependent on the utilisation of the Markov property. This was seen to be true even for models that are based on microsimulation or discrete event simulation (DES), which do not need the need for this assumption. The evolution of diseases is a multifaceted phenomenon, and the incorporation of dependence structures that utilise historical data is frequently crucial in constructing simulation models that accurately reflect reality. One possible approach to tackle this matter could involve the utilisation of random effects, as suggested by Karnon et al. [20] Models can be formulated in a manner that ensures the Markov assumption is valid, given a certain set of random effects that are not directly seen.

Although mathematical models provide significant potential, they are not devoid of obstacles. The challenges surrounding data quality and availability continue to be of utmost importance. The precision of model predictions is dependent upon the calibre and volume of input data. Maximising the utility of these models necessitates the assurance of data integrity and accessibility. In addition, it is important to note that model validation is a continuous process. To ensure the reliability and accuracy

of model-driven decisions, it is imperative to establish standardised validation techniques.

Ethical considerations assume significant importance, particularly within the realm of personalised treatment. The utmost importance is in safeguarding privacy, ensuring informed consent, and upholding appropriate practises in the utilisation of patient data. The establishment of explicit ethical rules and regulations is of utmost importance in order to effectively manage the utilisation of sensitive medical information within the context of mathematical modelling.

The seamless integration of mathematical models into clinical practise is crucial in order to fully harness their potential. Healthcare practitioners greatly benefit from the utilisation of Clinical Decision Support Systems (CDSS) that integrate these models. Nevertheless, the achievement of successful integration necessitates more than just the establishment of technology infrastructure. It also calls for comprehensive training and education programmes to guarantee that healthcare practitioners possess the necessary skills to accurately understand and use insights obtained from models in the context of actual patient care.

The potential for mathematical modelling to play a significant role in predicting drug dosage and assessing efficacy is highly encouraging. Continuing research is expected to further improve current models, incorporate novel methodologies, and deepen our comprehension of intricate pharmacological mechanisms. Enhanced data gathering techniques, such as the incorporation of real-world evidence, will serve to enhance the precision and reliability of these models. Furthermore, it is imperative to emphasise the significance of multidisciplinary collaboration among mathematicians, doctors, and regulatory agencies in order to facilitate the ongoing advancement and acceptance of these models.

Conclusions

The use of mathematical models into the domains of pharmacology and healthcare signifies a significant advancement, holding the potential to revolutionise drug development, patient care, and personalised medicine. As the conclusion of this examination of mathematical modelling approaches nears, it is vital to contemplate the significant ramifications, advancements, and obstacles that have arisen as a result of effectively utilising these models.

The utilisation of mathematical models has significantly transformed the approach to medication development. Physiology-based models have played a crucial role in facilitating the identification of safe starting doses, while pharmacokinetic and pharmacodynamic models have been important in optimising dosages for clinical investigations. The utilisation of these models has significantly expedited the drug development process and resulted in cost reduction. Through the facilitation of data-driven decision-making, chatbots have become essential assets in the pharmaceutical industry's pursuit of innovation and operational effectiveness.

In our research, we observed a relatively limited number of studies that successfully bridged the gap between the efficacy data derived from Randomized Controlled Trials (RCTs) and the real-world effectiveness of drug interventions using mathematical models. Despite this, our comprehensive review of relevant models and their applications offers valuable insights for readers aiming to develop a

deeper understanding of the current landscape of mathematical modeling in predicting the relative effectiveness of drug interventions within the realm of comparative effectiveness research.

A notable finding from our review is that many of the identified models, which successfully navigate the transition from efficacy to real-world effectiveness, are Markov multi-state models. While these models have proven effective in numerous instances, we recognize that they are not the sole approach available. Physiology-based models, though theoretically promising, come with their own set of challenges. The development of such models demands an extensive amount of information and substantial effort. These highly intricate structures may be most suitable for scenarios where copious data and comprehensive biological knowledge are readily accessible.

Looking ahead, we anticipate significant growth in predictive modeling within comparative effectiveness research. Both in terms of applications and methodological advancements, this field is poised for expansion. As technology continues to evolve and our understanding of biological processes deepens, we foresee a proliferation of innovative modeling approaches. This growth will be instrumental in informing healthcare decisions, optimizing treatment strategies, and ultimately improving patient outcomes.

In conclusion, our examination of the current landscape of mathematical modeling in comparative effectiveness research reveals opportunities for further exploration and innovation. While challenges exist, the potential impact of these models in bridging the gap between controlled clinical environments and real-world healthcare contexts is undeniable. We encourage researchers, clinicians, and policymakers to embrace and contribute to the burgeoning field of predictive modeling, as it holds the promise of enhancing the quality and effectiveness of healthcare interventions in the years to come.

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Информация об авторах / Information about the Authors

Shehine Mohamad Tufik, Associate Professor of the Department of Biological and Chemical Technology, Kursk State Medical University of the Ministry of Health of the Russian Federation, Kursk, Russian Federation,
e-mail: chahine@kursksmu.net,
ORCID: 0000-0001-8504-2418

Шехине Мохамад Туфик, доцент кафедры биологической и химической технологии, Курский государственный медицинский университет Министерства здравоохранения Российской Федерации, г. Курск, Российская Федерация,
e-mail: chahine@kursksmu.net,
ORCID: 0000-0001-8504-2418

Nikolaos Tzenios, Professor of Public Health and Medical Research, Charisma University, Grace Bay, Turks and Caicos Islands,
e-mail: chahine@kursksmu.net,
ORCID: 0000-0002-6679-2296

Тзениос Николаос, профессор общественного здравоохранения и медицинских исследований, Университет Харизмы, Грейс-Бей, острова Теркс и Кайкос,
e-mail: chahine@kursksmu.net,
ORCID: 0000-0002-6679-2296

Ksenia Viktorovna Zavidovskaya, Assistant of the Department of Biological and Chemical Technology, Kursk State Medical University of the Ministry of Health of the Russian Federation, Kursk, Russian Federation,
e-mail: knvz@mail.ru,
ORCID: 0000-0003-0786-4533

Ксения В. Завидовская, ассистент кафедры биологической и химической технологии, Курский государственный медицинский университет Министерства здравоохранения Российской Федерации, г. Курск, Российская Федерация,
e-mail: knvz@mail.ru,
ORCID: 0000-0003-0786-4533

Yulia Mikhailovna Dotsenko, Assistant of the Department of Biological and Chemical Technology, Kursk State Medical University of the Ministry of Health of the Russian Federation, Kursk, Russian Federation,
e-mail: yuliadoczenko@gmail.com,
ORCID: 0000-0001-8458-9083

Юлия М. Доценко, ассистент кафедры биологической и химической технологии, Курский государственный медицинский университет Министерства здравоохранения Российской Федерации, г. Курск, Российская Федерация,
e-mail: yuliadoczenko@gmail.com,
ORCID: 0000-0001-8458-9083

Lyudmila Petrovna Lazurina, Doctor of Science (Biology), Professor, Head of the Department of Biological and Chemical Technology, Kursk State Medical University Ministry of Health of Russia, Kursk, Russian Federation,
e-mail: lazurinalp@kursksmu.net,
ORCID: 0000-0003-1937-1453,
Scopus ID: 55924214100

Людмила П. Лазурина, доктор, биологических наук, профессор, заведующий кафедрой биологической и химической технологии, Курский государственный медицинский университет Министерства здравоохранения Российской Федерации, г. Курск, Российская Федерация,
e-mail: lazurinalp@kursksmu.net,
ORCID: 0000-0003-1937-1453,
Scopus ID: 55924214100