THEORETICAL AND CONCEPTUAL FOUNDATIONS OF CHRONIC MYELOID LEUKEMIA

V.E. Babakhanzada
Western Caspian University

Abstract: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterised by the uncontrolled proliferation and accumulation of myeloid lineage cells. As a malignant disorder, CML involves abnormal hematopoiesis and associated clinical manifestations. Over the past decades, significant advancements have been made in understanding and treating CML; however, further research is still required to elucidate its fundamental mechanisms and pathophysiology. The hallmark of CML is the presence of the Philadelphia chromosome, a genetic abnormality resulting from a translocation between chromosomes 9 and 22. This translocation leads to the formation of the BCR-ABL oncogene, which encodes a protein with constitutive tyrosine kinase activity, promoting uncontrolled cell proliferation and survival by evading apoptosis. CML progresses through three distinct phases: the chronic phase, the accelerated phase, and the blast crisis phase. In the chronic phase, symptoms are often mild and may be detected incidentally through routine blood tests. The accelerated phase is marked by worsening symptoms and an increased risk of progression to blast crisis, the most severe and life-threatening stage, which necessitates urgent intervention. Tyrosine kinase inhibitors (TKIs) represent the cornerstone of modern CML treatment. Drugs such as Imatinib have significantly altered the disease course, improving survival rates and patients' quality of life. However, drug resistance and adverse effects remain challenges, necessitating the exploration of alternative therapeutic strategies.

Keywords: Myeloid leukemia, Disease, Genetic, Chronic, Stem Cell.

***Corresponding Author:** vusala.babakhanzada@gmail.com

Received: 15 December 2024; Accepted: 28 February 2025; Published: 30 March 2025

DOI: 10,54414/HTQV6902

Introduction:

Chronic myeloid leukemia (CML) is a malignant hematologic disorder that arises from the clonal expansion of myeloid cells. Over the past few decades, significant advances in molecular biology and genetics have contributed to an enhanced understanding of this disease. The role of molecular and genetic testing in the diagnosis and monitoring of CML has become increasingly important. Precision in the detection and quantification of key genetic markers, such as the Philadelphia chromosome and the BCR-ABL fusion gene, is crucial in managing the disease. These biomarkers provide not only a means for diagnosing CML but also a valuable tool for monitoring disease progression and evaluating the effectiveness of therapeutic interventions. The ability to detect BCR-ABL at varying levels allows clinicians to track the evolution of the disease over time and identify patients at risk for progression to more advanced stages.

In addition to monitoring disease progression, genetic tests can help identify

early signs of resistance to treatment. Resistance to tyrosine kinase inhibitors (TKIs), such as imatinib, is a major challenge in the management of CML, and molecular testing plays a vital role in identifying mutations in the BCR-ABL gene that may confer resistance. These mutations may be present in a small fraction of leukemic cells, making early detection essential for adjusting therapeutic strategies. Furthermore, the use of genetic testing allows for the personalization of treatment regimens, ensuring that patients receive the most appropriate therapy based on their unique genetic profile. This approach improves the chances of successful treatment and reduces the likelihood of unnecessary side effects caused by ineffective therapies.

In recent years, ongoing research has led to the discovery of additional genetic alterations and novel biomarkers in the genomes of CML patients. These genetic changes, such as mutations in signaling pathways and epigenetic regulators, have opened up new avenues for targeted therapies. By focusing on these additional genetic factors, researchers are identifying potential new therapeutic targets, which may allow for more effective and individualized treatment strategies. These findings highlight the complexity of CML and the need for continuous innovation in treatment approaches. The discovery of new biomarkers also holds promise for improving early diagnosis and better stratifying patients based on their prognosis and potential response to therapy.

The theoretical and conceptual foundations of CML have evolved significantly due to the rapid advancements in biotechnology and genetic research. The development of high-throughput sequencing technologies, which allow for comprehensive genomic analysis, has revolutionized our understanding of the molecular landscape of CML. These technologies have enabled the identification of novel mutations, gene expression profiles, and epigenetic changes that play a role in the pathogenesis of CML. Moreover, recent advances in gene editing tools, such as CRISPR-Cas9, offer the potential for more precise interventions at the genetic level, potentially leading to more effective treatments. These technological innovations, along with ongoing clinical trials, are driving the development of novel therapeutic agents and treatment strategies, which are expected to improve outcomes for patients with CML.

As the understanding of CML deepens, the development of new and more effective treatments continues to progress. These advancements aim to not only improve survival rates but also enhance the quality of life for patients living with the disease. Through ongoing research and collaboration between scientists, clinicians, and patients, the future of CML treatment looks promising. The continued evolution of molecular and genetic testing, along with novel therapeutic approaches, will pave the way for a more personalized and effective management of CML.

Materials and Methods:

The gene panel for chronic myeloid leukemia (CML) was developed by analyzing genetic data from patients diagnosed with CML. Bioinformatics tools were used to identify genetic variants and mutations associated with CML, focusing on genes linked to disease progression, treatment response, and drug resistance. The gene panel was designed to include both known and novel genetic variants for a comprehensive profile of each patient. Blood samples were collected from CML patients across multiple clinical centers, with informed consent obtained from all participants. Control samples were also included to establish baseline genetic profiles for comparison.

DNA was extracted from the blood samples using a commercial kit and assessed for quality and quantity. Next-generation sequencing (NGS) using Illumina platforms was employed to detect genetic variants, mutations, and polymorphisms. The sequencing data were aligned to the reference genome using the Burrows-Wheeler Aligner (BWA), and variant calling was conducted using the Genome Analysis Toolkit (GATK). Variants were annotated with databases such as dbSNP and ClinVar to identify known CML-related

mutations, and novel variants were classified based on in-silico tools to predict pathogenicity.

To validate the identified genetic markers, quantitative PCR (qPCR) and Sanger sequencing were used. These techniques ensured the accuracy of the variants found in both patient and control samples. Clinical data, including age, gender, disease stage, and treatment history, were gathered and correlated with the genetic findings. Statistical analyses, including Chi-square tests and logistic regression, were performed using SPSS and R software to assess the significance of the correlations between genetic markers and clinical outcomes.

The study was approved by institutional review boards (IRB), and informed consent was obtained from all patients. Data confidentiality and privacy were maintained by anonymizing patient information. Additionally, a clinical trial was designed to evaluate the effectiveness of personalized treatment strategies based on the gene panel's findings. Patients were stratified based on their genetic profiles, and personalized treatments were administered, with outcomes monitored to assess improvements in disease progression, treatment response, and survival.

Results and discussions:

XML research is part of our expanding knowledge base in cancer biology and will lead to greater advancements in managing the disease in the future. Furthermore, studies on chronic myeloid leukemia (XML) have increasingly started to incorporate scientific and computer technologies. The application of large data sets and complex statistical modeling enables deeper analysis of the genetic and molecular profiles of the disease. This approach allows for more accurate prognostic indicators and personalized treatment protocols, considering the specific characteristics of cancer in each patient. For instance, the application of artificial intelligence and machine learning technologies can predict the progression of the disease and response to treatment. These technologies assist in rapidly processing large volumes of variables associated with the disease, helping to identify differences between patients who respond to treatment and those who do not.

Chronic myeloid leukemia (XML) is a blood cancer that mainly develops due to genetic changes. The most significant cause of this disease is a genetic anomaly called the Philadelphia chromosome. This anomaly occurs as a result of a reciprocal translocation between chromosomes 9 and 22, leading to the formation of a hybrid gene known as BCR-ABL. The BCR-ABL gene codes for a continuously active tyrosine kinase protein, which promotes the uncontrolled growth and division of blood cells, disrupting the normal development and function of blood cells. Healthy blood cells are gradually replaced by cancerous ones. Other factors that can lead to the development of chronic myeloid leukemia include radiation exposure, such as during atomic bomb explosions or radiation accidents. However, such incidents rarely cause the disease, and genetic factors are still considered the primary cause.

The disease typically occurs in middle-aged and older adults, but exceptions can occur. It can even develop in children, although the highest-risk group consists of individuals aged 50-60. Moreover, innovations in clinical trial design and execution also promise significant advancements in XML treatment. Adaptive trial designs ensure real-time evaluation of data and optimization of treatment protocols.

Chronic myeloid leukemia (XML), though one of the rarer types of blood cancer worldwide, is influenced by the unique genetic characteristics of each ethnic and geographic group, playing a crucial role in its spread and treatment effectiveness. Although data on the genetic characteristics and prevalence of XML in the Azerbaijani population is currently limited, research in this field could improve the understanding of genetic predisposition and aid in personalizing treatment approaches. Investigating the genetic traits of XML in Azerbaijan, particularly the analysis of various BCR-ABL oncogene variants and mutations, is important to understand how the disease spreads in the local population and the response to treatment. Such research may also suggest

potential uses for various genetic markers in the early diagnosis of the disease (Куликов, 2014).

Genetic studies on chronic myeloid leukemia (XML) allow health institutions in countries like Azerbaijan to gain a deeper understanding of the local characteristics of cancer diseases and tailor treatment protocols accordingly. Expanding genetic research not only improves the effectiveness of treatment methods but also provides a foundation for reducing potential side effects and increasing patient survival rates. In this regard, genetic research conducted in Azerbaijan can assist in the identification of new biomarkers and targets for more accurate diagnostics, treatment personalization, and improved survival rates. For example, identifying genetic variants that cause resistance in some patients could play a crucial role in selecting alternative drugs or therapy combinations for these patients (Бутенко, 2001). Furthermore, such research allows for the real-time monitoring of biomarkers to evaluate the response to treatment. This helps in closely monitoring the progression of the disease and adjusting the treatment to suit the patient's current health status. Local genetic research contributes to optimizing XML treatment in Azerbaijan and achieving better outcomes for patients. This process benefits both patients and national health systems, as more effective treatment methods can reduce costs and improve patients' health and quality of life. Thus, local genetic research is critical in the fight against chronic myeloid leukemia, and investments in this area can offer substantial returns for the development of the healthcare sector (Кресова, 2014).

One of the most important treatment methods, Tyrosine Kinase Inhibitors (TKIs), has been a turning point in the treatment of XML. These drugs provide the possibility to slow the progression of the disease and improve patients' quality of life. However, some patients develop resistance to these drugs over time, which necessitates a reconsideration of treatment strategies (Куклев, 2016).

Immunotherapy and Stem Cell Transplantation are treatment options that offer alternative approaches, especially for advanced stages of the disease. Immunotherapy stimulates the patient's immune system to fight cancer. Stem Cell Transplantation, on the other hand, is a more radical treatment, often applied when other therapies fail, particularly in severe cases. Next-generation therapies include innovative approaches such as gene editing and targeted molecular interventions. These treatments offer promising alternatives, particularly for patients who have developed resistance to TKIs or have not benefited sufficiently from standard therapies. The collection and analysis of local data on the genetic characteristics and prevalence of chronic myeloid leukemia plays an important role in shaping healthcare policies in countries like Azerbaijan and the fight against the disease. This could also be an important step in providing more effective and accessible treatment options for patients (Туркина, 2017).

Bioinformatics analysis of chronic myeloid leukemia (CML) is a crucial tool for the in-depth study of the genes responsible for this disease. CML is a type of blood cancer mainly associated with the formation of the Philadelphia chromosome. This chromosome results from the fusion of the BCR and ABL1 genes. Bioinformatics plays a significant role in the analysis of these genetic alterations, in identifying gene expression profiles, and in predicting responses to treatment. With the development of genetic sequencing technologies, bioinformatics methods have opened new horizons in understanding the genetics and pathophysiology of CML (Жуков, 2000). Molecular-level analyses allow for a more precise identification of the biological foundations of the disease and its resistance tendencies to treatment. The improvement of the effectiveness of drugs, such as tyrosine kinase inhibitors (TKIs), which inhibit BCR-ABL kinase activity, and the reduction of their side effects, is based on the results of these analyses. Bioinformatics analyses provide essential information in identifying genetic variants and polymorphisms, as well as in tracking changes in gene expression and signaling pathways. As a result of these analyses, the relationship between the different biomarker profiles of CML patients and their

response to treatment becomes clearer. This enables doctors to design more targeted and individualized treatment strategies for each patient. The bioinformatics analysis of the genes responsible for CML ensures a better understanding of this serious disease and helps achieve progress in its treatment. These analyses play an important role in the treatment of genetic diseases and the development of large-scale research and clinical practices, opening new ways to increase patients' survival rates and improve their quality of life.

With the expansion of these genetic and molecular analyses, new biomarkers and potential therapeutic targets in the treatment of CML may also be discovered (Кресова, 2014). Through the bioinformatics analysis of CML genes, the molecular mechanisms of the disease are identified more accurately, providing a foundation for the improvement of treatment. For example, certain genetic variants or segments may exhibit resistance to treatment, in which case alternative drugs or therapeutic strategies could be applied. Progress in bioinformatics and molecular biology allows for a better understanding of various aspects of the disease, including genetic predispositions, disease progression, and response to treatment. This knowledge also plays a crucial role in the design and implementation of clinical trials, as these trials can target more precise patient groups and evaluate the effectiveness and safety of specific treatment types (Андросова, 1996). Bioinformatics analyses also encourage the development of innovative approaches in the treatment of CML, such as gene therapies and targeted treatments. For instance, gene editing technologies can be used to correct disease-related genetic defects and restore healthy cell functions.

The bioinformatics analysis of genes responsible for chronic myeloid leukemia (CML) continues to create revolutionary changes in medical research and clinical practices. These advancements provide significant benefits in improving patients' survival rates and quality of life. At the same time, they contribute to the expansion of scientific understanding and the enhancement of healthcare service effectiveness. It enables doctors and researchers to assess the relative importance of each gene in the biological context of CML. The comparison of gene expression levels provides valuable information in the management of the disease and the development of new treatment strategies. These analyses play a crucial role in evaluating the effects of drugs such as tyrosine kinase inhibitors (TKIs) in the treatment of chronic myeloid leukemia. For example, the "BCR-ABL" gene is recognized as the primary target for TKIs because its hyperactivity plays a critical role in the development of CML.

The accurate measurement of the expression levels of this gene forms the foundation for assessing the effectiveness of these drugs on the patient and evaluating the disease's progression. Additionally, the investigation of other genes such as "TET2," "ASXL1," and "DNMT3A" enables the creation of a more complex genetic portrait of CML (Fig. 1). These genes are associated with epigenetic modifications and cell differentiation. Their activity can influence treatment resistance and affect the course of the disease. Understanding the expression levels of these genes helps to further personalize treatment strategies and potentially discover new ways to overcome resistance. Moreover, this genetic data provides a foundation for uncovering the deeper biological mechanisms of cancer and improving treatment methods (Львов, 1989).

For example, specific genetic variants and mutations identified through bioinformatics analyses can reveal differences between various types and subtypes of the disease. Understanding these differences enables the offering of more suitable treatment options for patients and the development of personalized therapy strategies based on each patient’s needs. The creation of a new gene panel for chronic myeloid leukemia (CML) represents a significant advancement in the diagnosis, treatment, and management of this disease. CML is a type of blood cancer in which genetic factors play a crucial role, and the key genetic event that causes this disease is the BCR-ABL gene fusion (Fig. 2). A new gene panel, which includes this and other genetic markers, can ensure faster and more accurate detection of the disease and facilitate the development of

personalized treatment approaches (Куликов, 2014). This new gene panel will cover genes related to CML, including resistance variants and other genes potentially involved in treatment response. It will provide a deeper insight into the biological and molecular profile of the disease and help make treatments more targeted and effective. For example, based on the specific genetic profile identified by the gene panel, stronger tyrosine kinase inhibitors may be prescribed for some patients, while gentler treatment methods may suffice for others. The application of this gene panel will also be valuable for clinical research because it will allow a better understanding of various aspects of the disease. The discovery of new biomarkers and therapeutic targets in the fight against the disease may be faster and more effective due to this panel. This innovation will play a significant role in improving survival rates and quality of life for CML patients. The implementation of the new gene panel will also assist in the early detection and monitoring of chronic myeloid leukemia (CML). Early diagnosis offers the opportunity to slow the disease's progression and achieve better treatment responses. This panel can provide the necessary genetic data to clarify the stages of the disease and make treatment options more targeted. For instance, the genetic variants identified by the gene panel play a key role in personalizing the treatment regimen (Кресова, 2014).

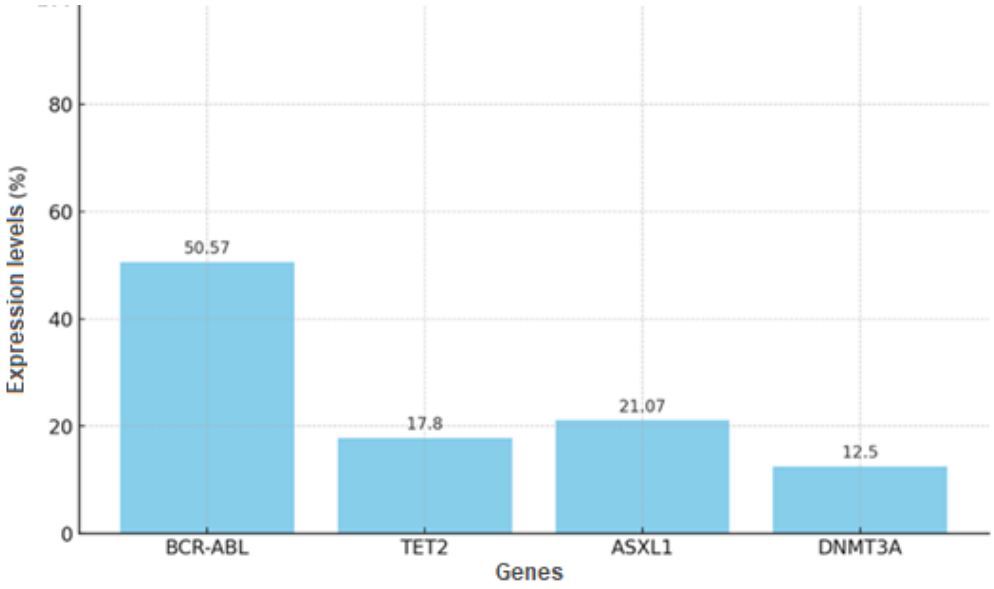

Fig. 1. Expression levels of genes responsible for chronic myeloid leukemia (Туркина, 2017).

Doctors can use this data to develop specific treatment protocols based on each patient's genetic profile. This approach is a crucial step in increasing the effectiveness of treatment and reducing side effects. Furthermore, the new gene panel will allow for a better understanding of cases resistant to treatment. Identifying resistant variants enables doctors to apply alternative treatment pathways promptly, which increases the patient's chances of survival. Additionally, studying resistance mechanisms lays the foundation for the development of new drugs and treatment strategies. The development and application of the gene panel will allow for a deeper understanding of the complex genetic and molecular dynamics of the disease. The comparison of gene expressions can help identify potential treatment targets and biomarkers, which can be used in the management of CML patients and further personalize treatment plans. The implementation of the new gene panel will allow for the development of more targeted approaches in the management and treatment of chronic myeloid leukemia (CML). This panel aims to increase the effectiveness of treatment,

reduce resistance, and minimize side effects. Based on gene expression data, doctors can tailor treatment plans more accurately, particularly by offering personalized therapies according to each patient's genetic characteristics. (Туркина, 2017).

Furthermore, the new gene panel will play a crucial role in the early diagnosis of CML. Accurate identification of genetic markers can ensure the detection of the disease in its early stages, which leads to more effective treatment at the outset. Early diagnosis not only increases the patient's chances of survival but also has the potential to reduce treatment costs. The new gene panel will also contribute to clinical research. Through this panel, the effects of various genetic variants on treatment can be studied comparatively. This information can help in better understanding the different variants of the disease and potentially lead to the development of new treatment methods. For example, if certain genetic profiles respond better to treatment, treatment strategies can be developed and tailored to those profiles. The new gene panel will lead to revolutionary changes in CML research and treatment. These advancements will offer significant innovations to improve survival rates, enhance treatment effectiveness, and improve the quality of life for patients. By providing researchers and doctors with new insights and treatment options, this development will open a new chapter in the battle against CML (Туркина, 2017).

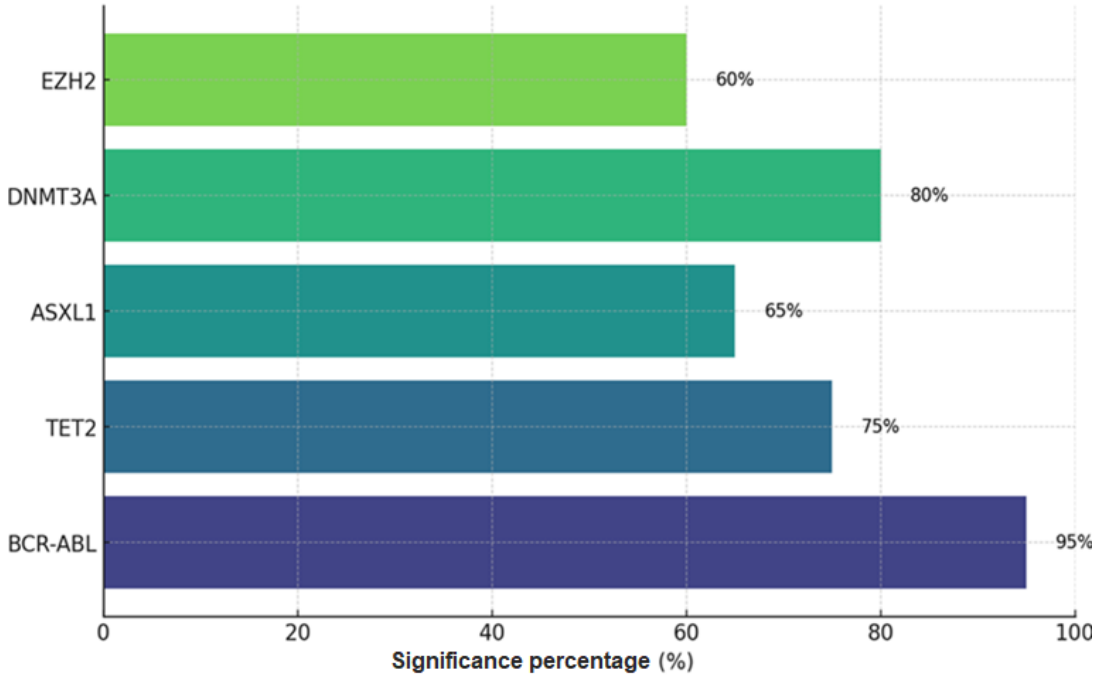

Fig. 2. Significance values of genes in the new gene panel for chronic myeloid leukemia (Куликов, 2014).

Conclusıon:

The newly created gene panel marks the beginning of a new era in research and treatment of chronic myeloid leukemia (CML). This panel provides a deep view of the disease at the genetic level and allows for the development of more effective treatment methods tailored to the genetic characteristics of each patient. Specifically, the precise identification of genes associated with CML is crucial for early diagnosis, improving treatment response, and managing resistance cases. This gene panel also helps in more targeted planning and implementation of clinical trials, providing a foundation for discovering new therapeutic targets. As a result, the application of this panel

creates a pathway for the development of effective treatment approaches that can increase survival chances and improve the quality of life for CML patients. Overall, the creation of this new gene panel is a significant advancement in the fight against chronic myeloid leukemia. Its widespread application in future research and clinical practice promises better outcomes for patients. These advancements will contribute to further improvement in genetic and molecular research in the medical field and increase the effectiveness of large-scale healthcare services. Innovations also enable patients and their families to have a deeper understanding of the disease, allowing them to be more informed and actively participate in the treatment process. A better understanding of patients' genetic profiles ensures that disease-related decisions are made more transparently and personalized, thereby increasing patient satisfaction and treatment adherence. At the same time, the new gene panel provides healthcare policymakers with the opportunity to develop more informed strategies for managing chronic myeloid leukemia. This information helps healthcare systems manage their financial and resources more efficiently, as treatment methods can be applied more purposefully and effectively. In the future, further development and expansion of this gene panel will lead to greater progress in the fight against CML. The gene panel may expand to cover more genetic markers and biomarkers, allowing for a more precise biomolecular profile of the disease. These advancements will ensure a deeper understanding of diseases and the discovery of more effective treatment options. In conclusion, the creation of a new gene panel for chronic myeloid leukemia is considered a turning point in the management and treatment of the disease. This innovation marks a new phase in medical research and opens wide possibilities for improving patients' health outcomes. This is a valuable and significant advancement for both the scientific community and the general public.

References:

Куликов, С.М. et al. (2014) Заболеваемость хроническим миелолейкозом в 6 регионах Россиипо данным популяционного исследования 2009-2012 г. Терапевтический архив 86(7): 24–30.

Туркина, А.Г., Новицкая, Н.В. et al. (2017) Регистр больных хроническим миелолейкозом в Российской Федерации: от наблюдательного исследования к оценкеэффективности терапии в клинической практике Клиническая онкогематология 10(3): 390–401.

Туркина, А.Г. et al. (2017) Клинические рекомендации по диагностике и лечениюхронического миелолейкоза. Клиническая онкогематология 10(3): 294–316.

Андросова, С.В., Рогаткин, А.К. (1996) Изучение экологии арбовирусов и распространение природно - болезней на территории Астраханской области. Астрахань: 32.

Бутенко, А.М., Ковтунов, А.И., Джаркенов, А.Ф., Злобина, Л.В., Гришанова, А.П. et al. (2001) Эпидемиологическая характеристика лихорадки Западного Нила в Астраханской области. Вопросы вирусологии 4: 34–35.

Жуков, А.Н., Филиппов, А.Г., Краснова, Е.Н. (2000) Эпидемия лихорадки Западного Нила в Волгоградской области. ЗниСО 92(11): 9–10.

Жукова, Л.И., Рафеенко, Г.К., Городин, В.Н., Ванюков, А.А. (2016) Клинико-эпидемиологическая характеристика лихорадки Западного Нила в Краснодарском крае. Журнал микробиологии, эпидемиологии и иммунобиологии 2: 74–80.

Кресова, У.А., Гаранина, С.Б., Казакова, Л.В., Куклев, Е.В., Сафронов, В.А. (2014) Сочетанные очаги актуальных для Саратовской области природно-очаговых инфекционных болезней. ЗНиСО 255(6): 30–32.

Куклев, Е.В., Ковалевская, А.А., Ковтунов А.И. (2016) Критерии оценки потенциальной эпидемической опасности сочетанных природных очагов бактериальных и вирусных

инфекций. Материалы XIII Межгосударственной научно-практическойконференции, 1–2 ноября 2016 г.:Саратов: 136–137.

Львов, Д.К., Клименко, С.М., Гайдамович, С.Я. (1989) Арбовирусы и арбовирусные инфекции. – М: 335 с.

Mitelman F. Catalog of Chromosome Aberrations in cancer, 6th edn., 1998, Wiley-Liss, New York.

Mrozek K., Heerema N.A., Bloomfield C.D. Cytogenetics in acut leukemia. Blood Reviews, 2004, 18, 115–136.

Mrozek K., Heinonen K., Bloomfield C.D. Prognostic value of cytogenetic Finding in adults with acute myeloid leukemia. Int J Hematol, 2000, 72:261–271.

Mrozek K., Heinonen K., Bloomfield C.D. Clinical importance of cytogenetics in acute myeloid leukaemia. Bailliere's Clin Haematol, 2001, 14, 19 – 47.

Scandura J.M., Boccuni P., Cammenga J., Nimer S.D.. Transcription factor fusions in acute leukemia: variations on a theme. Oncogene, 2002, 21:3422– 44. 29. Shaffe