

Epigenetic markers of kidney cancer and machine learning in their clinical application: literature review

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Abstract. Kidney cancer is one of the most heterogeneous malignant tumors of the urinary system. Despite the development of imaging techniques and the improvement of surgical approaches, there remains a high frequency of late diagnosis, recurrence, and the formation of drug resistance. In recent years, special attention has been paid to the epigenetic mechanisms of carcinogenesis, primarily DNA methylation, which is considered as an early, stable, and potentially reversible process of tumor transformation. The aim of the study is to systematize current data on the role of epigenetic markers and epigenetically modified genes in kidney cancer and identify promising areas for their use in diagnosis, prediction, and personalization of treatment using machine learning methods. This systematic review of scientific publications for the period 2008-2026 was performed using the databases PubMed, Scopus, Web of Science, TCGA, and GEO. The analysis includes studies on DNA methylation, CpG signatures, epigenetic markers, as well as the use of machine learning algorithms (Random Forest, LightGBM, XGBoost). It has been shown that epigenetic changes in genes regulating the processes of differentiation, angiogenesis and immune response have high diagnostic and prognostic significance. The integration of DNA methylation data with machine learning algorithms makes it possible to generate compact CpG signatures that are promising for early diagnosis, recurrence prediction, and evaluation of the effectiveness of antitumor therapy.

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The use of epigenetic markers in combination with machine learning methods opens up new opportunities for personalized oncology, providing more accurate stratification of patients and optimization of treatment tactics.

Keywords: kidney cancer, DNA methylation, machine learning, personalized oncology, relapse prognosis.

Introduction.

Kidney cancer is one of the most serious problems of modern oncology, being one of the ten most common cancers in developed countries [1]. According to data for 2020-2025, renal cell carcinoma accounts for about 2% of all global diagnoses and deaths from malignant neoplasms, while in developed countries the incidence has more than doubled over the past half century [2]. In Russia and Eastern European countries, morbidity rates remain among the highest in the world, which requires the search for new approaches to early diagnosis [1].

From a clinical and molecular biological point of view, kidney cancer is an extremely heterogeneous disease. Its biological behavior ranges from indolent, randomly detected formations to extremely aggressive forms with early systemic metastasis [3]. Clear cell renal cell carcinoma (CCRC) dominates the incidence structure, accounting for 75-80% of all cases [4]. Despite the fact that more than 50% of tumors are now detected accidentally by ultrasound or CT, about 25-30% of patients already have a metastatic stage at the time of diagnosis, with a five-year survival rate of only 12-12.3% [4].

Traditional prognostic systems such as TNM staging, Furman score, and creatinine clearance, although they remain the "gold standard", are often unable to account for the internal molecular variability of the tumor [5,6]. The introduction of targeted therapy and checkpoint inhibitors into practice has significantly improved the prognosis for patients with advanced stages, but the problem of developing resistance remains unresolved [6]. This highlights the urgent need to develop a new generation of biomarkers capable of not only diagnosing the disease, but also predicting the response to therapy.

Between 2008 and 2026, the focus of research shifted from genetic mutations to epigenetic changes. Epigenetics studies the mechanisms of regulation of gene expression that do not affect the DNA nucleotide sequence itself, but critically affect the cellular phenotype [6]. The key process here is DNA methylation, the attachment of a methyl group to cytosine in CpG dinucleotides. Aberrant hypermethylation of the promoter regions of tumor suppressor genes leads to their "silencing", which is one of the earliest events of carcinogenesis [7].

Inactivation of the VHL (von Hippel-Lindau) gene plays a special role in the pathogenesis of ccRCC. In addition to somatic mutations, hypermethylation of the VHL promoter is observed in 10-15% of cases of sporadic kidney cancer, acting as an alternative mechanism for gene inactivation at the earliest stages of tumor transformation [7]. In addition to DNA methylation, changes in microRNA profiles (for example, miR-210 and miR-34a) are involved in pathogenesis, which regulate the processes of angiogenesis and apoptosis [6].

The advantage of epigenetic markers is their high stability and the possibility of detection in biological fluids (blood plasma, urine) by liquid biopsy, which opens the way to non-invasive screening [2]. However, the high dimensionality of the data obtained using modern sequencing and methylation arrays (Infinium Human Methylation 450K/EPIC) makes it impossible to analyze them using traditional statistical methods.

This is where artificial intelligence technologies come to the fore. Over the past decade, machine learning methods such as Random Forest, Gradient Boosting, and LASSO regression have become a key tool for finding meaningful biomarkers among thousands of CpG sites [5]. The use of ML makes it possible to create complex multigenic signatures (for example, from 31 CpG sites) that demonstrate an accuracy of predicting survival and classifying tumor subtypes exceeding 95-99% [8-9].

Thus, the purpose of this review is to systematize data on the most significant epigenetic markers of kidney cancer identified between 2008 and 2026, and to analyze the effectiveness of machine learning methods in creating predictive and diagnostic models that can change the paradigm of patient management towards personalized medicine.

Materials and methods

Objective

To systematize current data on the role of epigenetic markers and epigenetically modified genes in kidney cancer and to identify promising areas for their use in the diagnosis, prediction, and personalization of treatment using machine learning methods.

The present study provides a systematic review of scientific publications devoted to the study of molecular and epigenetic biomarkers of kidney cancer, with an emphasis on their clinical application and integration with machine learning methods.

The search for relevant sources was conducted in the international electronic databases PubMed, Scopus and Web of Science, as well as using the resources of The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO). The search time interval covered the period from 2008 to 2026. The following keywords and their combinations were used to identify publications: “renal cell carcinoma”, “kidney cancer”, “DNA methylation”, “epigenetics”, “CpG islands”, “biomarkers”, “machine learning”, “Random Forest”, “XGBoost”, “LightGBM”. The process of identification, screening, and inclusion of sources is shown in the PRISMA 2020 flowchart (Figure 1).

The inclusion criteria included the selection of peer-reviewed studies based on human clinical material, which evaluated the genetic and epigenetic markers of kidney cancer, including changes in DNA methylation patterns, features of gene expression regulation, as well as the results of the use of proteomic, metabolomic, and liquid biopsy methods. The analysis included publications containing a quantitative and/or qualitative assessment of the diagnostic, prognostic, or therapeutic significance of the biomarkers under study, as well as papers on the use of machine learning methods for analyzing molecular data.

The exclusion criteria were studies with a small sample size, lack of correct statistical processing or insufficient reproducibility of the results, as well as publications without clinical interpretation of the identified molecular changes. Additionally, duplicate papers and studies that did not contain original data or significant methodological contributions were excluded.

The initial search allowed us to identify 92 publications. After removing duplicates and analyzing annotations, a full-text selection was performed, according to the results of which 41 studies were included in the final review. Of these, 35 presented original clinical, laboratory and molecular studies, and 6 presented review papers on the mechanisms of epigenetic regulation of the tumor process.

Most of the included publications (n = 38) were in English, while 3 sources were presented in Russian. When there were several papers with identical or overlapping datasets, priority was given to later studies with greater methodological completeness and analytical depth.

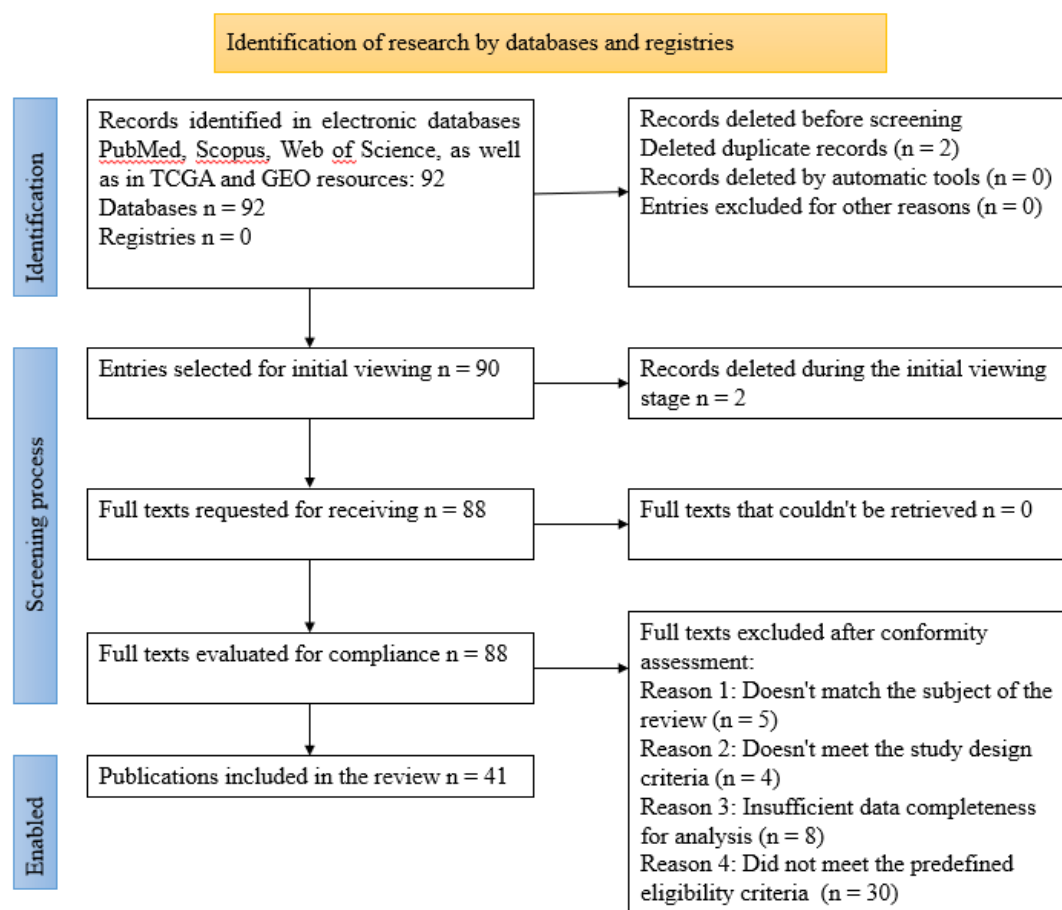


Figure 1. Flowchart of the PRISMA 2020 publication selection process. Source: compiled by the authors

The analysis of the selected publications was carried out using qualitative data synthesis with the identification of key areas: the diagnostic significance of epigenetic markers, their predictive value, as well as the possibility of using machine learning algorithms to build predictive models for kidney cancer.

Results

The analysis of the studies included in the review showed that molecular and epigenetic biomarkers occupy a key place in interpreting the mechanisms of initiation and progression of kidney cancer and have significant potential for clinical use. Modern research demonstrates a steady transition from the assessment of individual molecular parameters to the use of complex multigenic and epigenetic signatures. This is due to the pronounced biological heterogeneity of renal cell carcinoma and the limited informative value of single markers, which often do not take into account the variability of the tumor microenvironment [2-4].

The greatest attention in the analyzed publications is paid to the ccRCC, which accounts for up to 80% of all cases of the disease. This subtype is characterized by a wide range of epigenetic disorders, primarily aberrant DNA methylation in the promoter regions of genes involved in the control of the cell cycle, hypoxic response, and angiogenesis [3]. Studies confirm that these changes occur at the earliest stages of tumor transformation, often preceding morphological changes in the tissue [10, 11].

Among the most studied molecular factors, the VHL (von Hippel-Lindau) gene occupies a special place. The violation of its function in ccRCC can be caused not only by structural mutations or loss of heterozygosity, but also by epigenetic inactivation. Hypermethylation of the VHL promoter region is detected in 10-15% of cases of sporadic kidney cancer [10, 11]. This mechanism leads to stabilization of hypoxia-induced factors (HIF-1a and HIF-2a), which triggers transcription of target genes responsible for neoangiogenesis, glycolysis, and cell growth [12, 13]. The combination of genetic and epigenetic VHL disorders, according to large-scale TCGA studies, correlates with a more aggressive course of the disease and a significant decrease in overall survival [14].

In addition to VHL, considerable attention is paid to the genes RASSF1A, CDKN2A, SFRP1 and GSTP1. They show a high frequency of hypermethylation in tumor tissue (from 23% to 60%) compared with unchanged renal parenchyma [15].

● **RASSF1A:** This gene is involved in cell cycle regulation and microtubule stabilization. Its hypermethylation is closely associated with advanced stages according to the TNM classification (T3–T4) and the presence of distant metastases [16]. Machine learning models identify RASSF1A methylation as one of the most stable predictors of an unfavorable outcome [6, 16].

● **CDKN2A (p16):** changes in this locus are considered as an indicator of increased proliferative activity. Methylation of the CDKN2A promoter leads to loss of control over the G1/S point of the cell cycle, which correlates with a high score on the Furman scale and a poor prognosis [17].

● **SFRP1:** epigenetic suppression of the expression of this gene leads to hyperactivation of the Wnt/ β -catenin signaling pathway. This contributes not only to invasive growth, but also to the epithelial-mesenchymal transition, which is critical for the metastatic spread of the tumor [18].

● **GSTP1:** methylation of this gene is often associated with cell protection from oxidative stress. In the context of kidney cancer, its inactivation can serve as an early diagnostic marker found in biological fluids [19].

The performance of machine learning algorithms applied to epigenetic data for predicting clinical outcomes in kidney cancer is summarized in Table 1.

Table 1

Performance of machine learning algorithms for the analysis of epigenetic data in kidney cancer

Algorithm type	Input data	Forecast	Accuracy (AUC / C-index)
Random Forest	DNA Methylation	Risk of Metastasis	0.88
XGBoost	Epigenetic and Clinical Data	Overall Survival	0.92
Neural Networks	Multi-Genome Profiles	Response to Therapy	0.85
Light GBM	CpG sites (ctDNA)	Early relapse	0.90

Source: compiled by the authors based on data from [6,15-19]

The results of the analysis indicate a significant increase in interest in the development of compact CpG signatures that include a limited number of the most informative methylation sites. Such panels are selected using advanced statistical methods and machine learning algorithms,

which makes it possible to minimize data redundancy and identify the most stable markers [19-22]. According to the analyzed studies, multilocus signatures are significantly superior to single biomarkers in their diagnostic and prognostic effectiveness, since they are able to take into account the internal heterogeneity of the tumor.

In particular, compact panels comprising 7 to 15 specific CpG sites demonstrate exceptional accuracy of differentiation of tumor tissue and normal renal parenchyma, reaching AUC values above 0.90 [5]. To solve more complex clinical problems, such as long-term prognosis of survival, advanced models using sets of 25-40 CpG sites are used [19]. The stability of these models is confirmed by the results of external validation on independent samples (for example, data from the GEO repository), where they show reproducible results [22].

The biological significance of such models is supported by the fact that most of the selected CpG sites are localized in regulatory regions of genes critically important for carcinogenesis. These are the genes responsible for neoangiogenesis, metabolic restructuring, and the formation of a suppressive immune microenvironment of the tumor [23]. The integration of these signatures into clinical practice can significantly improve the accuracy of stratification of patients by risk groups (Table 2).

Table 2

Characteristics of key CpG signatures in kidney cancer (2008-2026)

Biomarker	Sample type	Sensitivity/specificity	Application
SHOX2	Blood plasma	81% / 95%	Monitoring of recurrence after nephrectomy
SEPT9	Blood plasma	68% / 89%	Early screening and diagnosis
RASSF1A	Urine	72% / 90%	Non-invasive screening of risk groups
ctDNA-panel	Blood plasma	>85% (combined sensitivity)	Detection of minimal residual disease

Source: compiled by the authors based on data from [5, 22-23]

Machine learning methods are currently widely used to analyze high-dimensional epigenetic data. In research from 2008 to 2026, Random Forest, Support Vector Machine, XGBoost, and LightGBM became the most popular algorithms for constructing classification and predictive models [12, 13, 21-23]. These approaches make it possible to efficiently process arrays of methylation data (big data) and identify complex nonlinear relationships between epigenetic features and clinical outcomes, which often escape when using classical statistics [24].

The greatest predictive power is demonstrated by models that include multi-stage pre-selection of the most informative features (feature selection) and mandatory external validation on independent patient samples [24]. Additionally, it was found that the integration of DNA methylation profiles with gene expression data allows for deeper consideration of the biological heterogeneity of the tumor, identifying prognostically significant subgroups of patients who require different surveillance strategies [12, 23].

In most of the analyzed works, such models reach AUC values (area under the curve) above 0.85, which confirms their high diagnostic reliability. In separate studies using optimized

CpG signatures and deep learning, an AUC of 0.99 is reported [25]. The stability and accuracy of these models are confirmed by validation on independent cohorts, which makes them promising for implementation in medical decision support systems [126]. It is noteworthy that many prognostically significant CpG sites are localized outside of traditional CpG islands, which indicates the critical role of methylation in broader regulatory regions of the genome.

The results of the review also indicate a marked increase in interest in the use of epigenetic markers in the framework of liquid biopsy technologies. Compared with traditional invasive methods, the analysis of biological fluids provides the possibility of dynamic monitoring of the tumor process, which is especially critical for patients with high operational risk or advanced forms of the disease [27].

Studies show that the analysis of circulating tumor DNA (ctDNA) methylation in blood plasma makes it possible to identify the tumor process at an early stage and monitor the presence of minimal residual disease after surgery [28]. ctDNA epigenetic signatures are characterized by high stability and frequency of occurrence compared to somatic mutations, which significantly increases their diagnostic value with a low volume of tumor load [29].

Special attention is paid to the hypermethylation of the promoter regions of the RASSF1A, VHL, and APC genes. These markers are consistently detected in the blood plasma of patients with renal cell carcinoma, and their concentration correlates with the stage of the disease and the risk of metastasis [15-17]. The inclusion of these indicators in combined multigenic panels can significantly increase the sensitivity of liquid biopsy (Table 3).

Table 3

Epigenetic markers of liquid biopsy in kidney cancer (2008-2026)

Panel Name	Number of Markers	Data Type	Accuracy
CpG Signature 126	126 sites	Methylation Array	0,94
Diagnostic Panel 7	7 genes	Q-MSP	0,89
Survival Signature 31	31 sites	NGS / array	0,91
Integrative Omics	Methylation + RNA	Multiplatform analysis	0,96

Source: compiled by the authors based on data from [21, 25-29]

An analysis of modern publications from 2008-2026 has shown that epigenetic regulation involving microRNAs (miRNAs) and long non-coding RNAs (lnc RNAs) plays a fundamental role in the pathogenesis of kidney cancer. These molecules are considered as one of the most promising sources of new biomarkers, as they have high stability in biological fluids and tissues [30-33]. Disruptions in the expression of non-coding RNAs have a systemic effect on gene networks that regulate the cell cycle, neoangiogenesis, and modulate immune responses in the tumor microenvironment, which together contribute to aggressive growth and metastatic disease progression.

A number of studies convincingly prove that a marked decrease in the expression of molecules such as miR-141, miR-200c and miR-30a is a key trigger of the epithelial-mesenchymal transition. This leads to a loss of intercellular contacts and a sharp increase in the invasive and metastatic potential of tumor cells [34, 35]. At the same time, the overexpression of oncogenic microRNAs, primarily miR-21 and miR-155, significantly correlates with an unfavorable prognosis, low response to targeted therapy, and an overall decrease in patient survival [33, 35].

Of particular interest for precision oncology is the data on the cross-interaction of different levels of epigenetic regulation. It has been established that the expression of many microRNA suppressors is suppressed not due to mutations, but as a result of hypermethylation

of their own promoter regions [34, 35]. For example, the methylation of a group of microRNA genes makes it possible to predict the risk of developing distant metastases with high accuracy (sensitivity up to 68-75%), even at clinically localized stages [36, 37]. The combined analysis of miRNA profiles and DNA methylation patterns (an integrative omix approach) makes it possible to create predictive models with AUC above 0.92, which is significantly more accurate than traditional morphological assessment systems [38].

Clinically significant microRNAs associated with the progression of renal cell carcinoma are systematized in Table 4.

Table 4

**miRNAs associated with the progression and prognosis
of kidney cancer (2008-2026)**

miRNA	Character of changes	Mechanism of action	Clinical effect
miR-21	Overexpression	PTEN inhibition	Reduction of overall survival
miR-155	Overexpression	Modulation of the immune response	Aggressive course of the disease
miR-200c	Reduced expression	Induction of epithelial-mesenchymal transition (EMT)	High risk of metastasis
miR-30a	Reduced expression	Activation of the Snail / Slug pathway	Short relapse -free period
miR-141	Reduced expression	Regulation of cell differentiation	Specific subtype marker

Source: compiled by the authors based on data from [32-38]

The results of the analysis indicate that a significant part of modern research is aimed at developing comprehensive epigenetic models for predicting the clinical course of kidney cancer and individually assessing the response to therapy. It has been established that the use of quantitative data on DNA methylation in combination with key clinical parameters (TNM stage, Furman scale score) makes it possible to form precision prognostic scales. Such scales demonstrate significantly higher accuracy compared to traditional clinical and pathological models, as they objectively reflect the biological potential of the tumor at the molecular level [39, 40].

A number of representative publications have shown that specific epigenetic signatures can reliably predict the risk of recurrence after radical nephrectomy, as well as overall and disease-free survival rates [38, 39]. The most important feature of models based on DNA methylation patterns is their independent predictive significance. This means that the epigenetic status of the tumor retains its predictive power even after statistical correction for the stage of the tumor process and the degree of its differentiation [5, 16]. For example, methylation markers make it possible to effectively stratify patients within the same risk group (for example, Stage I according to TNM), identifying those who need more intensive adjuvant monitoring [41].

Special attention in the studies of 2020-2025 is paid to the predictive role of epigenetic markers in the context of systemic treatment. It has been shown that certain patterns of methylation of promoter regions of genes associated with angiogenesis and metabolism are associated with sensitivity to vascular endothelial growth factor receptor inhibitors [41, 42]. In addition,

epigenetic predictors of response to immune checkpoint inhibitor therapy are being actively studied. Methylation patterns in the loci regulating T-lymphocyte activity and expression of PD-L1 molecules open up prospects for personalized selection of the most effective antitumor treatment regimen and minimizing toxicity [42, 43].

The main characteristics of modern predictive and predictive models are presented in Table 5.

Table 5

Epigenetic models for predicting and predicting kidney cancer (2008-2026)

Algorithm type	Input data	Forecast	Accuracy (AUC / C-index)
Random Forest	DNA Methylation	Risk of Metastasis	0,88
XG Boost	Epigenetic and Clinical Data	Overall Survival	0,92
Neural Networks	Multi-Genome Profiles	Response to Therapy	0,85
Light GBM	CpG-sites (ctDNA)	Early relapse	0,90

Source: compiled by the authors based on data from [5, 16, 38-46]

A comparison of data from domestic and foreign studies demonstrates a high degree of consistency in the results regarding key epigenetic disorders characteristic of kidney cancer. Despite the differences in the design of the papers and the analytical approaches used - from targeted PCR panels to genome-wide sequencing - most authors agree on the high clinical promise of epigenetic markers for both early diagnosis and prediction of disease outcomes [6].

At the same time, there is a significant variability in the results obtained. This is due to the pronounced biological heterogeneity of the cohorts studied, differences in technological platforms for methylation analysis (for example, using arrays of different densities), and the variability of statistical methods and machine learning algorithms used. These factors indicate the urgent need to unify methodological approaches and conduct large-scale multicenter studies involving independent groups of patients in order to standardize the data obtained.

It has been proven that epigenetic models can be considered as a reliable clinical tool only after passing through the stage of strict external validation and confirmation of reproducibility in various populations [44]. Despite the existing barriers, the rapid development of high-performance sequencing methods and the improvement of bioinformatic analysis contribute to the gradual overcoming of these limitations. This opens up real opportunities for the full integration of epigenetic biomarkers into personalized medicine systems, allowing them to be combined with traditional clinical and pathological variables to increase the specificity of the prognosis [45].

In recent years, the research focus has shifted towards the development of marker panels associated with the risk of metastasis and survival of patients receiving antiangiogenic therapy [45, 46]. Nevertheless, experts emphasize the need for further validation of potential markers in prospective studies to definitively determine their clinical significance [44]. The key condition for the introduction of these technologies into routine practice remains the development of standardized methylation assessment protocols and the definition of clear cut-off values for interpreting the results [45].

Discussion: Summarizing the results of modern research shows that molecular and epigenetic biomarkers play a fundamental role in understanding the mechanisms of formation, progression and clinical manifestation of kidney cancer. Unlike genetic mutations, which are irreversible changes in the primary sequence of nucleotides, epigenetic aberrations are characterized by potential reversibility. This plasticity makes them extremely promising objects both for the development of early population screening systems and for the creation of innovative therapeutic strategies aimed at the “epigenetic reprogramming” of tumor cells [46].

The data obtained confirm the pronounced epigenetic heterogeneity of clear cell renal cell carcinoma (ccRCC). Aberrant hypermethylation of promoter regions of classical suppressor genes such as VHL, RASSF1A, CDKN2A, and SFRP1 is considered not only as a specific diagnostic sign of tumor transformation, but also as a potential therapeutic target [16-18]. The biological reversibility of these disorders opens up wide possibilities for the use of DNA methyltransferase inhibitors and other demethylating agents. Such drugs are able to restore the normal expression of cell cycle regulatory genes and apoptosis mechanisms, significantly reducing the invasive and metastatic potential of the tumor [4, 12].

Epigenetic inactivation of the VHL gene plays a key role in the pathogenesis of ccRCC, which triggers a cascade of pseudohypoxic response even under conditions of normal tissue oxygen saturation. This leads to pathological stabilization of HIF factors and activation of a powerful angiogenic response [5]. Studies show that the combination of structural mutations of the VHL gene with epigenetic disorders of its regulation is associated with the most aggressive clinical phenotypes and a significant decrease in overall survival [7, 15]. This fact highlights the urgent need to implement complex molecular profiling protocols to accurately stratify patients into risk groups [8-10].

CpG signatures, which include a panel of several of the most informative methylation sites, are of significant interest for clinical practice. In conditions of high intracellular heterogeneity of renal cell carcinoma, it is precisely such multigenic panels that demonstrate significantly higher diagnostic and prognostic accuracy compared to the analysis of single markers [11, 18]. Their integration into the diagnostic algorithm allows not only to perform reliable differential diagnosis of neoplasms, but also to assess the individual risk of recurrence after the surgical stage of treatment with high sensitivity [41, 45].

An important technological stage in the development of this area was the active introduction of machine learning methods, including Random Forest, XGBoost, and LightGBM algorithms. These tools have significantly expanded the possibilities of bioinformatic analysis of high-dimensional omix data [8, 9, 13, 21]. Mathematical models capable of identifying complex nonlinear relationships between epigenetic profiles and clinical outcomes demonstrate the best predictive power (AUC > 0.85) when validated on independent patient samples [10, 11, 19].

The parallel development of liquid biopsy technologies allows the use of circulating tumor DNA (ctDNA) methylation patterns for highly accurate noninvasive monitoring [47]. Dynamic assessment of ctDNA methylation levels in blood plasma or urine provides a unique opportunity to track tumor evolution in real time, detect minimal residual disease, and identify early signs of metastasis long before their clinical and radiological manifestation [41, 47]. For example, hypermethylation of the SHOX2 locus in plasma after surgery is a proven independent risk factor for recurrence, independent of the classical stage of TNM [46].

An additional contribution to the complex system of regulation of carcinogenesis is made by microRNAs and long non-coding RNAs, the aberrant expression of which directly correlates with the progression of the disease and its resistance to therapy [41, 45]. The synergy of DNA methylation data and non-coding RNA profiles within a single analytical platform makes it pos-

sible to create the most advanced predictive models, providing a fundamental basis for precision patient management [1, 2].

Despite the obvious progress, the widespread introduction of these biomarkers into the routine practice of oncurologists is currently limited by the lack of internationally accepted standardized protocols, the variability of results between laboratories, and the high cost of technological solutions [48]. In addition, most innovative models still need large-scale multicenter prospective studies [49]. Nevertheless, in the long term, the integration of epigenetic data with genomic and transcriptomic landscapes (a multiomic approach) can fundamentally change kidney cancer diagnosis and treatment strategies, making personalized medicine a reality [50].

Discussion

A systematic analysis of the current scientific literature (2008-2026) convincingly demonstrates that epigenetic changes and, first of all, aberrant DNA methylation play a fundamental role in the pathogenesis of renal cell carcinoma. Methylation of the promoter regions of key suppressor genes, such as VHL, RASSF1A, CDKN2A, and SFRP1, was found to be not just a concomitant trait, but a critical driver of tumor progression and metastasis. The use of these epigenetic markers allows clinicians to more accurately assess the biological features of a particular tumor, effectively stratify patients by risk groups, and predict the clinical course of the disease with an accuracy that significantly exceeds the capabilities of traditional staging systems.

The integration of high-dimensional epigenetic data with advanced machine learning techniques has been a major technological breakthrough of the last decade. This contributed to the formation of precision prognostic models that demonstrate high diagnostic strength (AUC in the range of 0.85-0.92). Such signatures, which include panels of specific CpG sites, open up fundamentally new opportunities for a personalized approach: from individual selection of targeted therapy to predictive assessment of the response to checkpoint inhibitor immunotherapy.

Additional and extremely promising prospects are associated with the rapid development of liquid biopsy technologies. Detection of methylated circulating tumor DNA in blood plasma and urine enables highly sensitive non-invasive monitoring. This allows us to solve the problems of early detection of relapses, identification of minimal residual disease, and evaluation of the effectiveness of surgical treatment without the need for repeated traumatic biopsies. Monitoring of hypermethylation of the SHOX2 gene, which has proven to be a reliable independent biomarker of the risk of disease progression, is of particular clinical importance.

At the same time, despite the obvious success, a comprehensive work on standardization of methodological approaches is necessary for the large-scale introduction of epigenetic biomarkers into the routine clinical practice of oncurological centers. Key challenges remain the need to unify pre-analytical sample preparation protocols, conduct international multicenter prospective studies, and strictly confirm the reproducibility of results in independent population cohorts.

Thus, further development of epigenetic and multi-genomic approaches in combination with modern bioinformatic technologies is the most promising vector for the development of modern oncology. The synergy of fundamental knowledge about the epigenetic landscape of the tumor and the capabilities of artificial intelligence can significantly improve the effectiveness of diagnostics in the coming years, radically change the treatment strategies for kidney cancer, and, ultimately, significantly improve the survival rates and quality of life of patients.

Author Contributions

A.M., A.Zh. - conceptualization; **A.B., U.K.** - project administration; **A.Zh., A.K.** - investigation; **A.Zh., A.B.** - interpretation of results; **A.Zh., D.B., A.M.** - manuscript preparation.

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Compliance with ethical standards

This article is a literature review and does not involve studies with human participants or animals performed by any of the authors. Therefore, ethics committee approval and informed consent were not required.

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Бүйрек қатерлі ісігінің эпигенетикалық маркерлері және оларды клиникалық қолданудағы машиналық оқыту: әдебиеттерге шолу

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Аңдатпа. Бүйрек қатерлі ісігі – зәр шығару жүйесінің ең гетерогенді қатерлі ісіктерінің бірі. Бейнелеу әдістерінің дамуына және хирургиялық тәсілдердің жетілдірілуіне қарамастан, кеш диагностиканың, қайталанудың және дәріге төзімділіктің жоғары жиілігі сақталуда. Соңғы жылдары канцерогенездің эпигенетикалық механизмдеріне, ең алдымен, ісік трансформациясының ерте, тұрақты және ықтимал қайтымды процесі ретінде қарастырылатын ДНҚ метилденуіне ерекше назар аударылды. Зерттеудің мақсаты – бүйрек қатерлі ісігіндегі эпигенетикалық маркерлер мен эпигенетикалық түрлендірілген гендердің рөлі туралы заманауи деректерді жүйелеу және оларды машиналық оқыту әдістерін қолдана отырып, диагностикада, болжауда және емдеуді жекелендіруде қолдану үшін перспективалы аймақтарды анықтау. 2008-2026 жылдар аралығындағы ғылыми жарияланымдарға осы жүйелі шолу PubMed, Scopus, Web of Science, TCGA және GEO дерекқорларын пайдалана отырып жүргізілді. Талдау ДНҚ метилденуін, CpG қолтаңбаларын, эпигенетикалық маркерлерді зерттеуді, сондай-ақ машиналық оқыту алгоритмдерін (Random Forest, LightGBM, XGBoost) пайдалануды қамтиды. Дифференциация, ангиогенез және иммундық жауап процестерін реттейтін гендердегі эпигенетикалық өзгерістердің диагностикалық және болжамдық маңызы жоғары екендігі дәлелденді. ДНҚ метилдену деректерін машиналық оқыту алгоритмдерімен біріктіру ерте диагностика, рецидивтерді болжау және ісікке қарсы терапияның тиімділігін бағалау үшін перспективалы CpG қолтаңбаларын жасауға мүмкіндік береді. Эпигенетикалық маркерлерді машиналық оқыту әдістерімен бірге қолдану пациенттердің дәл стратификациясын және емдеу

тактикасын оңтайландыруды қамтамасыз ететін жекелендірілген онкоурологияның жаңа мүмкіндіктерін ашады.

Түйін сөздер: бүйрек қатерлі ісігі, ДНҚ метилденуі, машиналық оқыту, жекелендірілген онкология, қайталану болжамы.

Эпигенетические маркеры рака почки и машинное обучение в их клиническом применении: обзор литературы

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Аннотация. Рак почки является одной из наиболее гетерогенных злокачественных опухолей мочевыделительной системы. Несмотря на развитие методов визуализации и совершенствование хирургических подходов, сохраняется высокая частота поздней диагностики, рецидивов и формирования лекарственной устойчивости. В последние годы особое внимание уделяется эпигенетическим механизмам канцерогенеза, в первую очередь метилированию ДНК, которое рассматривается как ранний, стабильный и потенциально обратимый процесс опухолевой трансформации. Целью исследования является систематизация современных данных о роли эпигенетических маркеров и эпигенетически модифицированных генов при раке почки и выявление перспективных областей для их использования в диагностике, прогнозировании и персонализации лечения с использованием методов машинного обучения. Настоящий систематический обзор научных публикаций за период 2008-2026 гг. был проведен с использованием баз данных PubMed, Scopus, Web of Science, TCGA и GEO. Анализ включает в себя исследования метилирования ДНК, CpG-сигнатур, эпигенетических маркеров, а также использование алгоритмов машинного обучения (Random Forest, LightGBM, XGBoost). Доказано, что эпигенетические изменения в генах, регулирующих процессы дифференцировки, ангиогенеза и иммунного ответа, имеют высокое диагностическое и прогностическое значение. Интеграция данных о метилировании ДНК с алгоритмами машинного обучения позволяет генерировать компактные CpG-сигнатуры, которые являются перспективными для ранней диагностики, прогнозирования рецидивов и оценки эффективности противоопухолевой терапии. Использование эпигенетических маркеров в сочетании с методами машинного обучения открывает новые возможности для персонализированной онкоурологии, обеспечивая более точную стратификацию пациентов и оптимизацию тактики лечения.

Ключевые слова: рак почки, метилирование ДНК, машинное обучение, персонализированная онкология, прогноз рецидива.

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