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ROLE OF MOLECULAR BIOMARKERS IN ADENOCARCINOMAS: DIAGNOSTIC, PROGNOSTIC AND THERAPEUTIC IMPLICATIONS

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Abstract. *Adenocarcinomas, which arise from glandular epithelial cells, represent the most common histological type of carcinoma that can be found in many organs such as the lungs, breast, colon, stomach, and pancreas. In modern oncology, molecular biomarkers are key component of precision (personalized) medicine, enabling an individualized approach to cancer diagnosis and treatment. The development of highly sensitive molecular technologies, such as next-generation sequencing (NGS), has significantly improved the identification of somatic and germline mutations of clinical importance. Today, tumor molecular profiling is increasingly used to detect specific biomarkers that serve not only as diagnostic tools, but also support therapy decision-making, monitoring of treatment response, and recurrence detection. This review summarizes the most commonly used molecular biomarkers in clinical practice for various adenocarcinomas, including EGFR, KRAS, BRAF, HER2, BRCA, MSI, and others. Special emphasis is placed on their role in diagnosis, treatment, and prognosis assessment, as well as on modern therapy strategies based on the presence of specific biomarkers. The aim of this paper is to highlight the significance of molecular biomarkers in personalized treatment approaches for adenocarcinomas and to contribute a better understanding of their clinical application. The available literature was reviewed using databases such as PubMed, ScienceDirect, and Google Scholar.*

Key words: *adenocarcinoma, biomarker, targeted therapy, gene mutation, EGFR, ROS, HER2*

Introduction

According to the definition provided by the National Cancer Institute, adenocarcinoma is "A cancer that forms in glandular tissue, which lines certain internal organs and produces and releases substances such as mucus, digestive juices, and other fluids. Most of the breast, lung, esophagus, stomach, colon, rectum, pancreas, prostate, and uterus cancers, are adenocarcinomas" [1]. Cancer is the second leading cause of death in the United States, and the leading cause of death among individuals under the age of 85. According to estimates by the American Cancer Society, approximately 2,041,910 new cases of invasive cancer are expected to occur in the United States in 2025, which equals about 5,600 cases per day [2]. Certain

adenocarcinomas produce substances during tumor development that aid in cancer screening, early diagnosis, prognosis, recurrence detection, and therapy monitoring [3]. Molecular tumor biomarkers are specific molecules such as genetic variants, epigenetic changes, transcriptional or protein alterations which are detectable in blood, urine, tissue, or liquid biopsy samples. Advances like NGS, nanotechnology, and circulating tumor DNA/RNA analysis have greatly improved their detection [4]. The use of biomarkers is highly important not only in personalized medicine but medicine in general. An ideal biomarker should be easily measurable with a simple, affordable, and minimally invasive test. It is also important to note that certain biomarkers can serve multiple purposes; for example, the same biomarker can be used as a diagnostic tool while also providing prognostic information [5]. It should also be emphasized that a single biomarker almost never provides a precise prediction of disease prognosis, risk of developing a condition, or other specific functions. Therefore, scientists and clinicians must carefully and critically evaluate analytical data when using and interpreting biomarkers [6].

Clinical application of molecular biomarkers in adenocarcinomas

Biomarkers in cancer are used to enable personalized medicine by improving risk assessment, early detection, diagnosis, prognosis, therapy prediction, and treatment monitoring. While traditional serum biomarkers like PSA, AFP, CA19-9, and CA125 are established, molecular biomarkers are increasingly valued for their diagnostic and therapeutic precision. Diagnostic biomarkers are used to confirm the presence of cancer or identify its subtype. Although diagnostic biomarkers can aid in cancer detection or patient classification by subtype, they are not sufficient for a final diagnosis and must be combined with other diagnostic methods, such as imaging or biopsy [7]. Prognostic biomarkers are used to determine the likelihood of clinical outcomes such as disease recurrence or progression. While this distinction is not universally accepted, prognostic biomarkers should be differentiated from predisposition/risk biomarkers, which relate to the transition from a healthy state to disease. Moreover, they differ from predictive biomarkers, which identify factors associated with the effect of an intervention or exposure [8]. Predictive biomarkers are factors associated with the initial response or resistance to a particular treatment. Predictive markers are especially important in oncology, as tumors originating from the same tissue can vary significantly in their response to most systemic therapies. The availability of predictive markers is expected to increase drug efficacy and reduce toxicity, enabling a more personalized approach to cancer treatment [9].

In the following sections, we will focus on molecular biomarkers most frequently discussed in the literature and commonly used in clinical practice for diagnosis, prognosis, and therapy of the most prevalent human adenocarcinomas.

Microsatellite Instability (MSI)

MMR (mismatch repair) is a DNA repair mechanism that corrects replication errors, maintaining genomic integrity. Loss of MMR activity causes accumulation of errors, leading to microsatellite instability (MSI). [10]. MSI is one of the few biomarkers approved for clinical use in colorectal carcinoma (CRC). MSI testing is currently

recommended for most patients following diagnosis of CRC, both for screening hereditary syndromes and due to its prognostic and therapeutic implications. MSI can currently be detected using two main approaches: immunohistochemistry (IHC)-based methods and polymerase chain reaction (PCR)-based methods [11]. Tumors are classified as MSI-high (MSI-H) if 30% or more of the loci show instability, as microsatellite stable (MSS) if no microsatellite markers show instability, and as MSI-low (MSI-L) if less than 30% of markers are unstable. The prognostic value of this biomarker is reflected in the following findings: MSI-H status predicts a favorable prognosis in early-stage colorectal cancer, with lower recurrence and better postoperative outcomes compared to MSS or MMR-proficient tumors. The predictive value lies in the fact that MSI-H tumors show a lack of benefit from 5-fluorouracil (5-FU), one of the most commonly used chemotherapy agents for treating colon cancer [12]. Additionally, MSI status is used for identifying patients with Lynch syndrome, the most common hereditary form of colorectal cancer. Furthermore, tumors with an MSI-H phenotype have shown favorable responses to PD-1 immune checkpoint inhibitors, such as pembrolizumab and nivolumab, further highlighting the clinical relevance of this biomarker [13].

HER2

Soluble Human Epidermal Growth Factor Receptor 2 (sHER2) is a biomarker for HER2-positive breast cancer at any stage [14]. HER2 positivity is currently defined as HER2 expression level by immunochistochemistry, IHC 3+, or IHC 2+ with gene amplification confirmed by in situ hybridization (ISH). Tumors with IHC 0, 1+, or 2+ without ISH amplification are considered HER2-negative [15]. In adjuvant clinical trials for breast cancer, HER2 positivity in early-stage disease has been identified as a biomarker for clinical outcomes and disease progression. Thus, in early-stage HER2-positive breast cancer, sHER2 has been shown to be a suitable prognostic biomarker for relapse and survival in patients who experience recurrence [14]. Overexpression of HER2 is associated with a more aggressive tumor phenotype and poorer prognosis. The predictive role of this biomarker lies in the fact that HER2-positive tumors respond better to trastuzumab therapy. Trastuzumab is the first HER2-targeted therapy approved by the U.S. Food and Drug Administration (FDA), and it is commonly prescribed in combination with chemotherapy [16]. The American Society of Clinical Oncology has recommended routine HER2 testing in patients with breast cancer. Previous studies have described the association between HER2 amplification and the benefit of adjuvant chemotherapy with doxorubicin, as well as doxorubicin plus cyclophosphamide followed by paclitaxel therapy in breast cancer. In a randomized trial, patients with HER2-positive breast cancer were also shown to benefit from anthracycline-based therapy [17].

BRCA1 and BRCA2

The BRCA1 and BRCA2 genes encode proteins that are well-known mediators in the DNA damage response, particularly in the repair of DNA double-strand breaks (DSBs) through homologous recombination (HR). Since the discovery of these genes in the early 1990s, it has been shown that individuals with germline mutations in BRCA1/2 genes have a significantly higher lifetime risk of developing malignancies

such as breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer, compared to the general population [18]. BRCA1 gene methylation is a process that involves the addition of a methyl group (CH_3) to DNA, specifically to the promoter region of the BRCA1 gene. This process can affect gene expression, meaning silencing its activity, which may increase the risk of cancer development. BRCA1 promoter methylation is a strong candidate as both a prognostic and predictive biomarker; however, intratumoral heterogeneity and differences in epialleles make BRCA1 promoter methylation only partially effective as a biomarker [19]. It is known that the dynamic evolution of tumors leads to different subpopulations of tumor cells with distinct genetic, epigenetic, and phenotypic characteristics. Different epialleles in these subpopulations may determine therapeutic response, as is the case with BRCA1 mutations. Scientists are now focusing their efforts on sequencing to capture all epialleles present in samples. The predictive role is reflected in findings from numerous studies showing that homozygous BRCA1 methylation predicts sensitivity to PARP inhibitors, while heterozygous methylation does not elicit the same response. This highlights the importance of analyzing BRCA1 methylation zygosity to predict clinical outcomes and guide therapy selection [20].

EGFR

The Epidermal Growth Factor Receptor (EGFR) is a transmembrane protein that belongs to the receptor family for ligands of the epidermal growth factor (EGF). Binding of EGF to EGFR stimulates cell growth and differentiation, regulating various processes including proliferation, migration, differentiation, apoptosis, and intracellular signaling during development [21]. Overexpression of EGFR is a frequent event in various tumors and is generally associated with more advanced disease stages, poorer prognosis, and higher mortality. There is some disagreement in the literature regarding whether increased EGFR gene copy number and overexpression affect the success of tyrosine kinase inhibitor (TKI) therapy. Recent studies have shown that patients with a high EGFR gene copy number (due to genetic amplification or chromosomal gains) and high EGFR protein levels respond better to drugs such as gefitinib and erlotinib. Mutations such as delE746_A750 and L858R are activating mutations and are associated with good responses to gefitinib or erlotinib [22]. According to the Catalogue of Somatic Mutations in Cancer (COSMIC) database, the most frequent deletions in exon 19 are delE746-A750 (68.9%), followed by delL747-P753insS (6.0%), delL747-T751 (4.1%), and delL747-A750insP (3.9%) [23]. It has been shown that patients with the 19del mutation have better outcomes compared to those with the L858R mutation or other rare mutations [24]. The L858R mutation is one of the most common oncogenic mutations in lung adenocarcinoma and is responsible for constitutive activation of EGFR, leading to unchecked tumor cell proliferation [25]. Gefitinib and erlotinib, both ATP-competitive inhibitors, show selectivity for the L858R mutant compared to the wild-type enzyme [26]. The T790M EGFR mutation was the first identified mechanism of acquired resistance to EGFR TKIs (gefitinib and erlotinib). It was discovered in 2005 when researchers analyzed patients with non-small cell lung cancer (NSCLC) who had EGFR mutations and progressed after initially responding to gefitinib or erlotinib. The T790M mutation increases drug resistance because cells harboring this mutation require significantly

higher drug concentrations for inhibition. Cell lines with the L858R-T790M mutation show much higher resistance to gefitinib and erlotinib than those with only L858R or exon 19 deletion, with T790M found in ~50% of patients with acquired resistance [27]. The T790M mutation is specifically targeted by the third-generation EGFR TKI drug osimertinib. For patients with the T790M mutation, osimertinib has provided significant survival benefits compared to cytotoxic chemotherapy and has been approved as the standard treatment [28]. These mutations are considered pharmacogenetic biomarkers that can predict therapeutic response, although patient response variability remains partially unexplained [22]. Rare EGFR mutations include G719X, S768I, and L861Q, which account for a small percentage of all EGFR mutations but may still have clinical relevance and respond to specific therapies. These mutations are considered "sensitive" to TKI therapy but are generally less responsive than classic mutations such as exon 19 deletions or the L858R mutation in exon 21. The S768I mutation (exon 20, <5% of EGFR mutations) and L861Q mutation (exon 21, ~2%) are linked to weaker responses to TKI therapy, though both can still show some treatment efficacy [29].

ALK

The anaplastic lymphoma kinase (ALK) gene is located on the short arm of chromosome 2, belongs to the insulin receptor superfamily, and encodes a protein. ALK mutations were first described in NSCLC in 2007 [30]. The Fluorescence in situ hibridization test (FISH) break-apart test is considered the gold standard for assessing ALK status and was the first approved diagnostic test for detecting ALK rearrangements through signal break detection. It remains the gold standard in NSCLC diagnostics. If the result is positive, treatment is carried out using ALK inhibitors [31]. ALK rearrangement, a structural change in the gene, was first described in anaplastic large cell lymphoma, where ALK fuses with the NPM gene. In the case of NSCLC, the most common ALK gene alteration is the fusion of its 3′ kinase domain with truncated portions of the EML4 gene, resulting from an inversion on the short arm of chromosome 2. This alteration leads to the constant activation of the ALK protein's kinase domain, independent of ligand binding. As a result, intracellular signaling pathways including AKT, MAPK, and JAK-STAT are activated, leading to uncontrolled cell growth, survival, and migration. In experimental conditions, when cells are engineered to express the EML4-ALK fusion protein, tumor formation (tumorigenesis) is induced, and tumor regression has been observed in mice treated with ALK inhibitors. ALK rearrangements are found in approximately 3% to 5% of lung adenocarcinomas, and affected patients are typically young and non-smokers, with no differences in ethnicity or gender. Adenocarcinomas with ALK rearrangement typically do not contain other oncogenic driver mutations. This means that if an ALK rearrangement is present, other mutations such as those in the EGFR or KRAS genes are unlikely to coexist [32].

ROS1

ROS1 gene fusions are genetic alterations associated with the development and progression of various types of cancer, particularly NSCLC. The ROS1 gene, located on chromosome 6, encodes a receptor tyrosine kinase that belongs to the proto-

oncogene family. Its exact physiological function is still not fully understood. In tumor cells, various ROS1 gene fusions can occur with partner genes, most often as a result of chromosomal aberrations. The most frequent fusions involve exons 43 or 44 of the ROS1 gene. The resulting fusion proteins possess constitutive kinase activity, leading to uncontrolled cell growth and proliferation. In NSCLC, the most common fusion is CD74–ROS1 (~44%), followed by EZR–ROS1 (16%), SDC4–ROS1 (14%), and SLC34A2–ROS1 (10%) [33]. Similar to ALK-positive patients, ROS1 fusions are mostly diagnosed in younger, non-smoking individuals. They account for approximately 1% of diagnosed NSCLC cases. The gold standard for diagnosis is FISH. ROS1 inhibitors are used as first-line treatment. ROS1 rearrangements are almost always mutually exclusive with alterations in EGFR, KRAS, BRAF, or ALK [34]. ROS1 gene rearrangements play an important role as predictive biomarkers in NSCLC, as they indicate a likely positive response to tyrosine kinase inhibitor therapy, similar to ALK-rearranged tumors. Although more common in advanced stages of the disease, these rearrangements are associated with a lower incidence of extrathoracic metastases, including brain metastases, which may also have prognostic implications for disease progression [35].

KRAS

The KRAS gene, specifically its mutations, are present in approximately 20–25% of NSCLC adenocarcinomas. The G12C locus mutation accounts for 43% of all KRAS mutations, followed by changes at the G12V locus (18%) and G12D locus (11%). The KRAS G12C mutation is one of the most common driver mutations in patients with lung adenocarcinoma, found in about 13% of patients in Western populations. KRAS gene mutations are highly dominant, which means that they tend to exclude other driver mutations and also persist within the tumor clone population over time [36]. KRAS gene mutations are most commonly located at codon 12, and less frequently at codons 13 and 61. Alterations in the KRAS gene lead to loss of GTPase activity, disrupting feedback regulation. As a result, KRAS continuously stimulates cell proliferation via the MAP kinase pathway (BRAF/MEK/ERK) and the phosphoinositide 3-kinase (PI3K) pathway. The G12C substitution is the most common alteration. In non-smokers with adenocarcinoma, the G12D substitution is found in 50% of all cases [37]. KRAS gene mutations are typically described as unfavorable biomarkers in patients with resected pulmonary adenocarcinoma. However, the prognostic implications of KRAS mutations remain controversial. Current studies have not demonstrated a definitive prognostic impact of KRAS mutations. KRAS mutations are considered a negative predictive biomarker for anti-EGFR therapy in colorectal cancer but have no effect on the efficacy of anti-EGFR antibodies in pulmonary adenocarcinoma. [38].

BRAF

The BRAF proto-oncogene is located on chromosome 7 and encodes a 766–amino acid protein involved in the EGFR/RAS/MAPK pathway. The normal BRAF protein alternates between active and inactive states, regulating cell growth and survival,

whereas the mutated form remains constitutively active, leading to uncontrolled cell proliferation and cancer development. The most common mutation is V600E, while other mutations are very rare [39]. Clinical data suggest that the presence of the BRAF V600E mutation is a negative prognostic factor in patients diagnosed with metastatic colorectal cancer, potentially indicating resistance to EGFR-antibody therapy, especially in patients who have already undergone intensive treatment. However, the predictive value of the BRAF V600E mutation in earlier lines of therapy remains uncertain [40]. BRAF gene mutations are found in up to 12% of CRC, with approximately 90% of these involving the V600E missense mutation, which substitutes valine for glutamic acid at codon 600. This mutation causes MEK pathway activation independent of KRAS. BRAF mutations are present in less than 10% of sporadic CRCs and in 31–83% of sporadic MSI-H tumors. Except for rare cases, RAS and BRAF mutations are mutually exclusive. Several studies have shown that CRCs that are wild-type for KRAS, NRAS, BRAF, and PIK3CA (quadruple-negative) have a higher likelihood of responding to targeted anti-EGFR therapy [41].

NRAS

Kristen-RAS (KRAS) and neuroblastoma-RAS (NRAS) belong to a type of G-protein known as the RAS superfamily. In normal cells, the RAS protein is inactive (bound to GDP) and can become active (bound to GTP) through various cell receptors. Half of all CRC cases contain activating mutations in KRAS and NRAS, often located in codons 12, 13, 59, and 61, which affect cancer cell metabolism and cause resistance to commonly used drugs [42]. NRAS and KRAS mutations share phenotypic traits, such as promoting tumorigenesis, but certain NRAS variants such as Q61K, can enhance tumor proliferation, while others, like G12D, may reduce proliferation and increase apoptosis [43]. Mutations in NRAS at codons 12 and 61 activate pathways including IL1, JAK/STAT, and NF-κB, which promote an inflammatory tumor microenvironment, enhance cell proliferation and survival, and thus contribute to therapy resistance. Mutant NRAS loses the ability to hydrolyze GTP, remaining permanently active, which triggers oncogenic signaling and makes it difficult to target due to its "undruggable" nature. Additionally, mutant NRAS protects colonic epithelial cells from stress-induced apoptosis. This anti-apoptotic role is mediated through the RAF-1 and STAT3 pathways, representing a unique mechanism that distinguishes NRAS from KRAS [44]. NRAS mutations are predictive biomarkers of resistance to anti-EGFR therapies (cetuximab, panitumumab) in metastatic colorectal cancer. Patients harboring NRAS mutations in codons 12, 13, 59, 61, 117, or 146 gain no clinical benefit from these agents, as the mutations activate EGFR-independent signaling pathways, leading to primary resistance [45].

DPYD

The DPYD gene encodes dihydropyrimidine dehydrogenase (DPD), the key enzyme responsible for degrading 5-fluorouracil (5-FU) into its inactive metabolite. Genetic variants that reduce DPD activity can cause accumulation of 5-FU, leading to severe treatment-related toxicity. Four DPYD alleles have been widely described as being

strongly associated with severe toxicity during fluoropyrimidine therapy, including rs75017182, rs55886062, rs3918290, and rs67376798 [45]. Fluoropyrimidines are widely used in the treatment of colorectal cancer and other solid tumors, with around 2 million patients treated annually. However, 10–40% of patients experience severe side effects, largely due to DPYD gene mutations that reduce DPD enzyme activity, leading to increased drug toxicity [46]. Pre-treatment pharmacogenetic testing for the four mentioned high-risk DPYD variants is recommended by several guidelines, as it enables early identification of patients at risk and supports personalized fluoropyrimidine therapy [47].

Conclusion

Biomarkers are key tools in modern oncology because they enable earlier diagnosis, selection of patients for targeted therapy, assessment of disease prognosis and prediction of therapeutic response. Their use leads to a personalized approach to treatment, which increases the effectiveness of therapy and reduces the risk of side effects. Within this paper, the most frequent molecular biomarkers of importance for adenocarcinomas are systematized, thus providing an overview of their diagnostic and therapeutic application in the context of personalized medicine. The primary clinical applications of biomarkers in adenocarcinomas mostly lie in their prognostic and predictive significance, which may be either favorable or unfavorable. Certain biomarkers, such as HER2, EGFR, BRCA, and BRAF V600E, are associated with more aggressive tumor phenotypes and poorer clinical outcomes, whereas others, such as MSI, correlate with more favorable prognoses. Beyond their prognostic value, biomarkers also play a pivotal role in guiding therapeutic decisions. For instance, ALK fusions indicate eligibility for ALK inhibitors, while BRCA mutations direct patients toward PARP inhibitors. Conversely, biomarkers can also exclude patients from therapies unlikely to be effective; a notable example is the presence of KRAS or NRAS mutations, which precludes the use of anti-EGFR therapy in colorectal cancer. A comprehensive understanding of biomarker functions is therefore essential for identifying patients most likely to benefit from targeted therapies, for recognizing those who require special attention due to potential drug toxicities (e.g., DPYD variants), and for selecting patients in whom immunotherapy demonstrates the greatest efficacy (e.g., MSI-H tumors). Consequently, determination of biomarker status constitutes a cornerstone in the selection process for personalized treatment strategies.

References

[1] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/adenocarcinoma pristupljeno 30.11.2024.
[2] Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. CA Cancer J Clin. 2025 Jan-Feb;75(1):10-45.
[3] Zhou Y et al. Tumor biomarkers for diagnosis, prognosis and targeted therapy. Signal Transduct Target Ther. 2024, 20;9(1):132.
[4] Sarhadi VK, Armengol G. Molecular Biomarkers in Cancer. Biomolecules. 2022, 23;12(8):1021.

[5] Struški P. Personalizirani pristup liječenju raka. Sveučilište u Zagrebu, Prirodoslovno-matematički fakultet, Završni rad, Zagreb 2022.
[6] Esmaeilzadeh A, Khosh E. Personalized immunology in cancer: paving the way towards a better quality of life. Multidiscip Cancer Investig. 2021;5(1):1–8.
[7] Sarhadi VK, Armengol G. Molecular Biomarkers in Cancer. Biomolecules. 2022, 23;12(8):1021.
[8] Melus C, Rossin B, Aure M A, Mahler M. Biomarker and data science as integral part of precision medicine, Precision Medicine and Artificial Intelligence, Academic Press, 2021, 65-96.
[9] Duffy MJ, O'Donovan N, Crown J. Use of molecular markers for predicting therapy response in cancer patients, Cancer Treatment Reviews, 37(2), 2011, 151-159.
[10] Vaish M, Mittal B. DNA mismatch repair, microsatellite instability and cancer. Indian J Exp Biol. 2002; 40(9):989-94.
[11] Yamamoto H, Watanabe Y, Maehata T, Imai K, Itoh F. Microsatellite instability in cancer: a novel landscape for diagnostic and therapeutic approach. Arch Toxicol. 2020;94(10):3349-3357.
[12] Battaglin F, Naseem M, Lenz HJ, Salem ME. Microsatellite instability in colorectal cancer: overview of its clinical significance and novel perspectives. Clin Adv Hematol Oncol. 2018 Nov;16(11):735-745.
[13] Ros J et al. Immunotherapy for Colorectal Cancer with High Microsatellite Instability: The Ongoing Search for Biomarkers. Cancers (Basel). 2023;15(17):4245.
[14] Kutomi G, Mizuguchi T, Satomi F, Maeda H. Current status of the prognostic molecular biomarkers in breast cancer: A systematic review. Oncology Letters 2017, 13(3):1495.
[15] Löb S et al. Prognostic effect of HER2 evolution from primary breast cancer to breast cancer metastases. J Cancer Res Clin Oncol. 2023;149(8):5417-5428.
[16] Gampenrieder SP et al. Landscape of HER2-low metastatic breast cancer (MBC): results from the Austrian AGMT_MBC-registry. Breast Cancer Res. 2021;23(1):112.
[17] Ding Y et al. The value of neoadjuvant anthracycline-based regimens for HER2-positive breast cancer: a systematic review and meta-analysis including 1366 patients. Clin Med Insights Oncol. 2023, 21;17:11795549231195293.
[18] Yamamoto H, Hirasawa A. Homologous Recombination Deficiencies and Hereditary Tumors. Int J Mol Sci. 2021, 29;23(1):348.
[19] Morizono, A., Tanabe, M., Ikemura, M. et al. Loss of BRCA1 expression and morphological features associated with BRCA1 promoter methylation status in triple-negative breast cancer. J Hum Genet, 2021, 66, 785–793.
[20] Panagopoulou M. et al. BRCA1 & BRCA2 methylation as a prognostic and predictive biomarker in cancer: Implementation in liquid biopsy in the era of precision medicine. Clin Epigenet. 2024, 16, 178.
[21] Bethune G, Bethune D, Ridgway N, Xu Z. Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update. J Thorac Dis. 2010;2(1):48-51.
[22] Jurišić V, Obradovic J, Pavlović S, Djordjevic N. Epidermal Growth Factor Receptor Gene in Non-Small-Cell Lung Cancer: The Importance of Promoter Polymorphism Investigation. Anal Cell Pathol (Amst). 2018, 14;2018:6192187.
[23] Su J et al. Molecular characteristics and clinical outcomes of EGFR exon 19 indel subtypes to EGFR TKIs in NSCLC patients. Oncotarget. 2017, 30;8(67):111246-111257.
[24] Le-Tian Huang, Shu-Ling Zhang, Cheng-Bo Han, Jie-Tao Ma. Impact of EGFR exon 19 deletion subtypes on clinical outcomes in EGFR-TKI-Treated advanced non-small-cell lung cancer, Lung Cancer, Vol 166, 2022, 9-16, ISSN 0169-5002
[25] Kanbour A et al. Leptomeningeal Metastatic L858R EGFR-mutant Lung Cancer: Prompt Response to Osimertinib in the Absence of T790M-mutation and Effective Subsequent Pulsed Erlotinib. Onco Targets Ther. 2022, 14;15:659-667.

[26] Ketan S et al. Insights into the Aberrant Activity of Mutant EGFR Kinase Domain and Drug Recognition, Structure, 2013, 21 (2), 209-219.
[27] Nguyen KS, Kobayashi S, Costa DB. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clin Lung Cancer. 2009;10(4):281-9.
[28] Zhao Z, Li L, Wang Z, Duan J, Bai H, Wang J. The Status of the EGFR T790M Mutation is associated with the Clinical Benefits of Osimertinib Treatment in Non-small Cell Lung Cancer Patients: A Meta-Analysis. J Cancer. 2020, 4;11(11):3106-3113.
[29] Zhang T, Wan B, Zhao Y, Li C, Liu H, Lv T, Zhan P, Song Y. Treatment of uncommon EGFR mutations in non-small cell lung cancer: new evidence and treatment. Transl Lung Cancer Res. 2019
[30] Shaw AT, Engelman JA. ALK in Lung Cancer: Past, Present, and Future. J Clin Oncol. 2013, 11;31(8):1105- 1111.
[31] Du X, Shao Y, Qin HF, Tai YH, Gao HJ. ALK- rearrangement in non-small-cell lung cancer (NSCLC). Thoracic Cancer. 2018 Feb 28;9(4):423–30.
[32] P Luk et al. Biomarkers for ALK and ROS1 in Lung Cancer: Immunohistochemistry and Fluorescent In Situ Hybridization. Arch Pathol Lab Med (2018) 142 (8): 922–928.
[33] Drilon A, Jenkins C, Iyer S, Schoenfeld A, Keddy C, Davare MA. ROS1-dependent cancers - biology, diagnostics and therapeutics. Nat Rev Clin Oncol. 2021;18(1):35-55.
[34] Muminovic M, Rodrigo C, Alvarez-Pinzon AM, Shan KS, Raez LE. Importance of ROS1 fene fusions in non-small cell lung cancer. Cancer drug resistance, 2023 6(2):332–44.
[35] Fois SS, Paliogiannis P, Zinellu A, Fois AG, Cossu A, Palmieri G. Molecular Epidemiology of the Main Druggable Genetic Alterations in Non-Small Cell Lung Cancer. Int J Mol Sci. 2021, 9;22(2):612.
[36] Ahmadzada T, Kao S, Reid G, Boyer M, Mahar A, Cooper WA. An Update on Predictive Biomarkers for Treatment Selection in Non-Small Cell Lung Cancer. Journal of Clinical Medicine, 2018, 7(6).
[37] Friedlaender A et al. Oncogenic alterations in advanced NSCLC: a molecular super-highway. Biomark Res, 2024, 12, 24.
[38] Calvayrak O. et al. Molecular biomarkers for lung adenocarcinoma. European Respiratory Journal 2017 49(4): 1601734.
[39] Preuzeto sa web sajta https://fightcolorectalcancer.org/biomarkers/braf/ pristupljeno 24.12.2024 u 17:16
[40] Cotan HT et al. Prognostic and Predictive Determinants of Colorectal Cancer: A Comprehensive Review. Cancers (Basel). 2024 Nov 23;16(23):3928.
[41] Requena DO, Buitrago MD, Molecular Insights Into Colorectal Carcinoma, Archives of Medical Research, 51(8), 2020, 839-844, ISSN 0188-4409.
[42] Lonescu A. et al. Multivariate Risk Analysis of RAS, BRAF and EGFR Mutations Allelic Frequency and Coexistence as Colorectal Cancer Predictive Biomarkers. Cancers 2022, 14(11), 2792.
[43] Kuhn N et al. Mutation-specific effects of NRAS oncogenes in colorectal cancer cells. Adv Biol Regul. 2021;79:100778.
[44] Duta-Ion SG. et al. Redefining Therapeutic Approaches in Colorectal Cancer: Targeting Molecular Pathways and Overcoming Resistance. Int. J. Mol. Sci. 2024, 25(23), 12507.
[45] Woolston A et al. Genomic and transcriptomic determinants of therapy resistance and immune landscape evolution during anti-EGFR treatment in colorectal cancer. Cancer Cell, 2019, 36(1), 35–50.e9.
[46] Henricks L et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. The Lancet Oncology, 2018, 19(11), 1459–1467.

[47] de Moraes, FCA et al. Pharmacogenetics of DPYD and treatment-related mortality on fluoropyrimidine chemotherapy for cancer patients: a meta-analysis and trial sequential analysis. BMC Cancer. 2024, 24, 1210.

ULOGA MOLEKULARNIH BIOMARKERA U ADENOKARCINOMIMA: DIJAGNOSTIČKE, PROGNOSTIČKE I TERAPIJSKE IMPLIKACIJE

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Sažetak. *Adenokarcinomi, koji se razvijaju iz žljezdanih epitelnih ćelija, predstavljaju najčešći histološki tip karcinoma koji se javlja u mnogim organima poput pluća, dojke, kolona, želuca i pankreasa. U savremenoj onkologiji, molekularni biomarkeri predstavljaju ključnu komponentu precizne (personalizovane) medicine, jer omogućavaju individualizovan pristup dijagnostici i terapiji karcinoma. Razvojem visokoosjetljivih molekularnih tehnologija, poput sekvenciranja nove generacije (NGS), značajno je unaprijeđena identifikacija somatskih i germinativnih mutacija koje imaju klinički značaj. Danas se molekularno profilisanje tumora sve češće koristi kako bi se odredila prisutnost specifičnih biomarkera koji sve više postaju alat ne samo za dijagnozu, već i za odluke o terapiji, praćenje efekta i otkrivanje recidiva. Ovaj pregledni rad prikazuje najčešće korištene molekularne biomarkere u kliničkoj praksi kod različitih adenokarcinoma, uključujući EGFR, KRAS, BRAF, HER2, BRCA, MSI i druge. Poseban fokus stavljen je na njihovu ulogu u dijagnostici, terapiji i procjeni prognoze, kao i na savremene terapijske pristupe zasnovane na prisustvu određenih biomarkera. Cilj rada je da prikaže značaj molekularnih biomarkera u personalizovanom pristupu liječenju adenokarcinoma i da doprinese boljem razumijevanju njihove kliničke primjene. Dostupna literatura procijenjena je iz baza podataka: PubMed, ScienceDirect i Google Scholar.*

Ključne riječi: *adenokarcinom, biomarker, targetirana terapija, genska mutacija, EGFR, ROS, HER2*