UDC: 616.34-006.6

DOI: 10.52532/2663-4864-2025-3-77-522

MULTIGENE TESTING IN GENETIC SCREENING OF HEREDITARY AND SPORADIC COLORECTAL CANCER: A LITERATURE REVIEW

N. BALTAYEV[1], G. AFONIN[1,2], G. ZHUNUSSOVA[3], D. KAIDAROVA[2], V. BELOUSSOV[4]

[1]Almaty Oncology Center, Almaty, the Republic of Kazakhstan;
[2]Asfendiyarov Kazakh National Medical University, Almaty, the Republic of Kazakhstan;
[3]Institute of Genetics and Physiology under the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan, Almaty, the Republic of Kazakhstan;
[4]Tree Gene Genetic Laboratory, Almaty, Republic of Kazakhstan

ABSTRACT

Relevance: *Molecular genetic testing to determine the patient's genotype and tumor molecular profile is a key component of a personalized approach to treatment and follow-up. Current research in genetic screening focuses on transitioning from phenotypic diagnostic panels and PCR testing of predisposition genes to large panels that include many identified genes or whole-genome sequencing. Multigene testing is widely used across colorectal cancer (CRC) diagnostics and therapy, where genetic components make a significant contribution. Currently, practical oncology requires a review of high-throughput sequencing systems for the genetic screening of hereditary and sporadic CRC variants and for the optimization of early diagnosis in relatives of patients.*

The study aimed to *review the methodology and current results of next-generation sequencing (NGS) applications for genetic screening of hereditary and sporadic colorectal cancer.*

Methods: *This analytical review included 70 original research and review articles available in open-access databases, including Google Scholar, Web of Science, SpringerLink, Scopus, ScienceDirect, PubMed, and BMJ.*

Results: *NGS-based multigene testing enables the simultaneous analysis of multiple genes involved in carcinogenesis, the identification of germline pathogenic mutations associated with hereditary tumor syndromes, and the detection of genetic variants in less-studied regions of genes, such as introns and untranslated regions, which help identify previously unknown factors predisposing to colorectal cancer.*

Conclusion: *Molecular genetic diagnostics facilitate personalized treatment of patients and individualized clinical examination of relatives from risk groups. However, although approximately 25% of CRC cases are familial, fewer than 5% of families are studied genetically. The analyzed data confirm the need to transition from phenotypic panels to comprehensive panels, encompassing all identified genes involved in hereditary tumor syndromes or whole-genome sequencing. In addition, identifying new variants with moderate and low penetrance, as well as those with uncertain functional significance, expands the phenotypic spectrum of CRC and necessitates further studies to determine their inclusion in diagnostic sequencing panels.*

Keywords: *Colorectal cancer (CRC), pathogenic mutations, next-generation sequencing, hereditary variants, genetic screening.*

Introduction: It has been established that approximately 25% of colorectal cancer (CRC) cases are associated with a family history of cancer or colorectal adenomas, and up to 5% arise in the context of hereditary cancer syndromes (HCS) with a relatively clear clinical picture and known causative mutations [1]. However, in the majority of cases, the genetic etiology of the disease remains unidentified. Families with clustering of CRC cases are heterogeneous with respect to phenotype, inheritance patterns, and lifetime cancer risk [2]. At the same time, establishing an accurate genetic diagnosis and identifying mutations significantly improves the effectiveness of early diagnosis and personalized treatment for patients, as well as the monitoring of conditionally healthy relatives [3]. The diagnosis of HCS influences therapeutic approaches (total/subtotal colectomy vs. segmental resection; choice of chemotherapy regimen) and follow-up care (colonoscopy and CT scan frequency; detection of possible extracolonic manifestations and metachronous tumors) [4]. Multigene testing (MGT) for conditionally healthy blood relatives of patients with familial and hereditary CRC is relevant, as it enables early diagnosis optimization. In Kazakhstan, only isolated studies based on next-generation sequencing (NGS) have been published to date, focusing on the frequency and spectrum of pathogenic germline mutations (GM) in patients and their relatives. At the same time, as shown, the proportion of Kazakhstani patients with a hereditary burden (HB) accounts for approximately 15% [5]. This underscores the relevance of implementing NGS testing in genetic screening and early diagnosis of CRC, as well as the interest in published data on methodology and results across different age and ethnic groups of patients.

The study aimed to review the methodology and current results of next-generation sequencing (NGS) appli-

cations for genetic screening of hereditary and sporadic colorectal cancer.

Materials and Methods: Original studies and review articles available in open-access academic databases were analyzed, including Google Scholar, Web of Science, SpringerLink, Scopus, ScienceDirect, PubMed, and BMJ, to review the approaches and results of MGT in genetic screening for CRC. A total of 114 sources were identified, of which 70 were included in the review. The selection criteria for articles were: the use of NGS as the primary experimental method with "hybrid" gene panels; the description of novel, previously unannotated mutations; and study designs that included young patients, patients with familial and hereditary forms of CRC, and relatives of patients.

Results: NGS-based multigene testing (MGT) enables the simultaneous analysis of multiple genes involved in carcinogenesis, the identification of germline pathogenic mutations leading to tumors or HCS [6-8], as well as the detection of genetic variants in less studied regions of genes, such as intronic and untranslated regions, which contributes to the identification of new, previously unknown cancer predisposition factors [9-11]. The use of "hybrid" diagnostic panels makes it possible to identify various types of genomic instability – copy number variations (CNVs), gene fusions, loss of heterozygosity (including copy-neutral LOH), ploidy, breakpoint detection, mosaicism, clonal heterogeneity, chromothripsis – as well as to assess the methylation status of oncogenes, tumor mutational burden, and microsatellite instability (MSI). These approaches are actively implemented in the comprehensive molecular genetic analysis of sporadic and hereditary CRC [12, 13].

As shown by S.A. Schubert et al., although approximately 25% of CRC cases are "familial", about 95% of individuals with HB do not undergo molecular genetic testing [2]. According to N.J. Samadder et al., in the United States, approximately half of CRC patients with clinically significant genetic variants (mutations) are not identified when diagnostics are based solely on standard clinical guidelines and criteria [14, 15]. Currently, even for researchers from countries with well-characterized populations, it remains unclear how many CRC patients and their relatives could benefit from NGS testing using large gene panels [16].

The concept of a *loss-of-function* (LoF) *mutation* is not equivalent to that of a *pathogenic mutation* or *pathogenic genetic variant* that leads to the phenotypic manifestation of a disease. The effect of the latter and its correlation with carrier status must be confirmed by case-control studies or functional assays [17]. Similarly, a distinction is made between established *cancer predisposition genes*, whose roles in carcinogenesis are clearly defined, and candidate genes, whose associations with tumor development are yet to be determined. The convergence of somatic and germline mutation profiles is well established in CRC genetics. For example, universal testing for mismatch repair (MMR) deficiency is a widely accepted approach to identify patients with germline mutations or Lynch syndrome (LS). While targeted testing of germline mutations in known genes can confirm a diagnosis of LS (or another specific HCS), large-panel sequencing detects GMs whose clinical significance is ambiguous and difficult to interpret.

In a comparative study of a heterogeneous group of Russian patients, A. Bilyalov et al., using a 44-gene panel, identified pathogenic variants (PVs) and likely pathogenic variants (LPVs) in 21.6% of patients with CRC, gastric cancer (GC), pancreatic cancer (PC), breast cancer (BC), and ovarian cancer (OC), with a mean age of onset of 44.5 years. Most of the mutations (39.4%) were detected in the *BRCA1* and *BRCA2* genes. The second most frequent were variants in the *CHEK2* gene (9.8%), and the third most frequent were variants in the *ATM* gene (6.3%), which were found in cases of PC and BC. In patients with CRC, the highest number of PVs was identified in the *MLH1* and *APC* genes. A previously unknown PV, c.160_166del in the *MLH1* gene – a 7 bp deletion in exon 2 – leads to the formation of a premature stop codon. In the same study, patients with multiple primary tumors (MPTs) were found to carry previously unannotated LPVs in the *MSH2* gene (c.893del and c.1729del) in a heterozygous state, resulting in a frameshift and formation of a premature stop codon [18].

It is well known that cancer risk and survival outcomes correlate with mutations in specific genes associated with LS. Although P. Møller et al. previously estimated the cumulative risk of CRC by age 75 to be 46% for carriers of heterozygous MLH1 mutations and 43% for carriers of heterozygous MSH2 mutations, the mean age at diagnosis, according to most publications, is 44 years [19]. Germline defects in MMR genes – *MLH1*, *MSH2*, *MSH6*, and *PMS2*, which form the molecular basis of LS – typically represent nucleotide-level changes within exonic sequences. These mutations induce generalized genomic instability, particularly at microsatellite loci. Loss of expression of *MLH1* and *MSH2* protein products, detected by immunohistochemistry (IHC), is used to identify patients with hereditary nonpolyposis colorectal cancer (HNPCRC) and germline mutations in the respective genes. It has been shown that the absence of known mutations or MSI in the tumor does not exclude a diagnosis of HNPCRC (so-called HNPCRC type X syndrome), and therefore necessitates sequencing to identify other germline mutations, as well as somatic mutations in the second allele or loss of heterozygosity [20].

Mutations in the *EPCAM* locus are associated with disruptions in cell migration, adhesion, proliferation, and signaling processes. It is known that 3'-deletions in *EPCAM* lead to hypermethylation of the MSH2 promoter, ultimately resulting in the phenotypic manifestation of LS. However, it remains unclear whether mutations in other re-

gions of *EPCAM*, including splicing regions, contribute to LS pathogenesis.

MLH genes are involved in maintaining genomic integrity during DNA replication and meiotic recombination. Studies on the association between germline MLH3 mutations and the development of HNPCRC have not established a clear link. Previously, H.X. Liu et al. demonstrated that *MLH3* is a low-penetrance gene. Furthermore, in a study of DNA isolated from tumor tissue, MLH3 mutations did not correlate with MSI levels, suggesting that this locus may not be involved in carcinogenesis by disrupting MMR mechanisms [21].

Recent publications report novel pathogenic variants in other MMR loci. M. Djursby et al., using a 32-gene panel, identified two variants in the *PMS2* gene in a cohort of young patients (under 40 years of age) [22]. The indel variant c.736_741delinsTGTGTGTGAAG/p.Pro246Cysfs*3 is annotated in the InSiGHT database as pathogenic and was previously identified in European patients [23]. The splice-site variant c.2275+1G>C, previously undescribed, was classified by the authors as an LPV based on results from long-range PCR, IHC, and *in silico* analysis. In the same study, a mutation in *MSH2* (c.2168C>T/p.Ser723Phe) was reported in a cohort of patients with familial forms of CRC. This variant had been previously identified in members of a family in Denmark and annotated in the InSiGHT database as a variant of uncertain functional significance. This variant was detected in a patient with MPTs – CRC (with loss of *MSH2* expression and unknown MSI status) and ampullary duodenal adenocarcinoma (with loss of *MLH1/PMS2* expression and *MLH1* promoter methylation). The HB pattern in this patient is of particular interest: early-onset CRC in the parents (44 years, non-carrier of the mutation in question) and extremely early-onset CRC in the offspring (25 years), who was a carrier of the mutation. Ser-723 is a highly conserved amino acid, and the c.2168C>T mutation is classified as pathogenic based on *in silico* analysis [22]. Previous studies using in vitro MMR models and human embryonic stem cells have demonstrated that this mutation disrupts MMR and is pathogenic [24, 25].

The *GALNT12* gene product participates in the catalysis of N-acetylgalactosamine (GalNAc) transfer from uridine diphosphate N-acetylgalactosamine (UDP-GalNAc) to a serine or threonine residue on a polypeptide acceptor. This reaction constitutes the first step of a type of post-translational modification known as O-linked protein glycosylation. K. Guda et al. suggested that germline loss-of-function mutations in *GALNT12* are associated with increased CRC risk [26]. The correlation between *GALNT12* PVs and CRC was further confirmed by D.R. Evans et al. [27].

Mutations in the tumor suppressor gene *APC* (nonsense or frameshift) lead to the formation of a premature stop codon and a functionally deficient protein. Loss of gene function may also result from hypermethylation. The *APC* gene, located on chromosome 5, encodes a protein that acts as a negative regulator of the evolutionarily conserved canonical Wnt signaling pathway. A key function of this protein is the cytoplasmic degradation of β-catenin: normally, this mechanism prevents its translocation into the nucleus, where it acts as a co-activator of transcription factors from the TCF/LEF family, thereby preventing uncontrolled cell division.

Several forms of familial adenomatous polyposis (FAP) are described, each characterized by different phenotypes. In Gardner-Turner syndrome, extracolonic manifestations are prominent (GI polyps, tooth anomalies, osteomas, cutaneous fibromas, and epidermoid cysts); in Turcot syndrome, brain tumors (e.g., medulloblastomas) occur. Correlations have been reported between mutation sites in the *APC* gene and corresponding clinical phenotypes. The classic form of FAP is caused by mutations in the central region of the gene, specifically between codons 168 and 1250, located closer to the 5' terminus. The diffuse form of FAP is observed in patients with mutations within codons 1285-1465. A missense variant, c.289G>A/p.Gly97Arg was described by M. Djursby et al. in siblings with the attenuated FAP (AFAP) phenotype, as well as in other family members [22]. This variant had previously been reported in AFAP patients in a study by D. Wang et al. [28]. The mutation leads to the formation of a cryptic splice acceptor site, disrupting normal splicing, and is annotated as an LPV.

Recently, a growing body of evidence has emerged regarding genetic alterations responsible for familial forms of CRC that are not related to HNPCRC or FAP. This category includes mutations in the *POLE*, *POLD1*, and *NTHL1* genes, identified through genome-wide association studies (GWAS) [29].

The *POLE* gene encodes the catalytic subunit of DNA polymerase epsilon, one of the four nuclear DNA polymerases involved in DNA repair. Homozygous pathogenic mutations in *POLE* cause autosomal recessive syndromes, such as FILS (OMIM #615139) and IMAGE-I (OMIM #618336) [18, 30-31]. According to P. Mur et al., germline PVs in *POLE* and *POLD1* are most frequently associated with CRC, endometrial cancer (EC), and OC [32]. Heterozygous variants in *POLE* that alter the structure of the exonuclease domain are associated with an increased risk of CRC. Further studies confirmed this association and identified numerous clinically significant pathogenic variants in *POLE* [33]. In the previously mentioned study, A. Bilyalov et al. described a novel LPV in *POLE* – c.802-2A>G – in a CRC patient. This variant represents a single-nucleotide substitution in the canonical splice site. According to the authors, the variant may lead to loss of function in the exonuclease domain or the entire protein [18]. M.F. Hansen et al. reported a PV in *POLE* c.1373A>T/p.Tyr458Phe was identified in three individuals from the same family. The inherited mutation c.824A>T/p.Asp275Val was

identified in a patient with OC and HB (CRC), and was initially considered a somatic alteration in EC, rather than a germline PV [34]. Previously, A. Rohlin et al. [35] and P. Vande Perre et al. [36] described the variant c.1089C>A/p.Asn363Lys in two large families with a phenotype including multiple tumors. The mutation affects the highly conserved amino acid Asn-363 in the exonuclease domain of POLE; however, to date, only missense variants in this domain have been considered pathogenic [37]. M. Djursby et al., who identified this same variant in a cohort of patients with very early-onset disease (under 40 years), reclassified it as a likely pathogenic variant based on *in silico* analysis and segregation data in families, as previously published by Rohlin and Vande Perre [22].

The serine/threonine kinase ATM is a member of the phosphoinositide 3-kinase-related protein kinase family and plays a critical role in the cellular response to DNA damage. Loss-of-function PVs in the *ATM* gene cause *ataxia-telangiectasia*, a rare autosomal recessive disorder characterized by neurodegeneration, increased radiation sensitivity, immunodeficiency, and cancer predisposition. Heterozygous carriers of germline PVs have an increased risk of developing various types of cancer, including BC [18, 38]. Hansen et al., using a 112-gene panel for sequencing, identified pathogenic germline mutations c.8494C>T/p.Arg2832Cys and c.8584+2T>C in patients with CRC – one of whom had a family history of BC, and the other had HB with synchronous tumors and polyposis. The same study also described patients with early-onset CRC and PVs in the *BRCA* genes. In carriers of BRCA1 c.4096+3A>G and BRCA2 c.2808_2811del/p.Ala938Profs*21, the family history included CRC, BC, and OC. Based on a segregation analysis within the family, the authors concluded that variant c.4096+3A>G in the patient and their first-degree relative is associated with CRC predisposition to a greater extent than with BC or OC [34].

In a cohort of Norwegian and Australian patients previously tested for LS, M.F. Hansen et al. described a PV in the *PTEN* gene in a patient with MPTs consistent with the Cowden syndrome spectrum [34]. The missense variant c.377C>T/p.Ala126Val is located in a highly conserved catalytic domain and, as shown by Costa et al., results in the formation of a completely inactive protein [39]. The *CHEK2* variant c.1100del/p.Thr367Metfs*15 was identified in a patient with early-onset CRC (age 37). This mutation has previously been described as being associated with BC, CRC, and prostate cancer.

In addition to variants in high-penetrance loci, NGS platforms are increasingly used to study mutations in moderate- and low-penetrance genes, such as *GALNT12* [23] and *EXO1* [40], as well as the effects of heterozygous PVs in autosomal recessive genes like *NTHL1* and *MSH3* [41, 42].

Discussion: NGS and GWAS are currently widely used to identify the etiology of familial CRC by detecting new candidate genes and PVs whose association with CRC has not yet been confirmed through case-control studies [43, 44]. In addition, whole-exome sequencing (WES) is applied to identify homozygous and polygenic mutations in cases of FAP, LS, or other familial forms of CRC [45, 46]. Polygenic variation has also been recognized as a potential cause of increased penetrance in LS [47]. The selection of candidate genes (panel design) for sequencing may be based on prioritization scores [48]; however, WES may also provide clinically significant information from non-coding regions of the genome. Using extended panels for WES, it is possible to expand the scope of analysis to include regions beyond exons, such as 5′ untranslated regions to capture transcription factor binding sites and reading frames, and 3′ untranslated regions to identify microRNA binding sites involved in gene regulation.

Mendelian inheritance syndromes account for approximately 5% of all CRC cases in which hereditary factors play an etiological role. These syndromes are caused by mutations and epimutations in well-studied predisposition genes, including MLH1, PMS2, MSH2, MSH6, EPCAM, APC, SMAD4, BMPR1A, STK11, MUTYH, PTEN, KLLN, PIK3CA, AKT1, POLE, POLD1, AXIN2, BUB1, and *BUB3*. It is not uncommon for a patient's personal or family history to require the simultaneous evaluation of multiple high-penetrance genes with known clinical impact – especially when clinical criteria for several syndromes are met within a single family (a phenomenon known as phenotypic overlap, often attributed to gene pleiotropy) [34], or when the patient presents with metachronous or synchronous tumors. When detailed family history is unavailable or when there is a high likelihood of a syndrome in individuals who do not meet standard diagnostic criteria, MGT is warranted. In clinical genetic counseling, patients with previous negative or inconclusive results from single-gene testing but with a clear familial predisposition to cancer should undergo NGS-based testing using multigene panels [49]. MGT is particularly clinically valuable in colorectal tumors with overlapping phenotypes, where differential diagnosis requires the analysis of multiple genes. For example, in Lynch syndrome, NGS may be more appropriate when IHC results are inconclusive.

In some families with FAP or LS-like features, no mutations are detected in *APC*, *MUTYH*, or MMR genes. Recently, mutations in *POLE*, *POLD1*, and other DNA repair genes have been identified in such families, leading to the diagnosis of "polymerase proofreading-associated polyposis" [37]. Considering the evidence of the functional significance of newly identified genes and the "phenotypic overlap" of the most common hereditary syndromes, as well as cases in which mutations in more than one gene may cause the condition, MGT represents a cost-effective approach to molecular genetic analysis and allows for the detection of mutations that are not identified through candidate gene testing [50]. Comprehensive genomic

profiling can be implemented in several formats: testing both tumor and normal tissue, testing tumor tissue only, or using circulating tumor DNA (the so-called "liquid biopsy"). For MGT performed using tumor-only DNA, the ESMO Precision Medicine Working Group (ESMO-PMWG) has proposed a PV filtering strategy to confirm germline origin. This strategy considers factors such as age at diagnosis, cancer type, the clinical significance of the gene, and the variant's allele frequency in tumor tissue [51]. The germline conversion rate for each gene is calculated as the ratio of germline PVs to the total number of PVs identified in the tumor.

In current molecular oncology practice, gene panels are used for targeted or broad NGS-based sequencing. Diagnostic panels allow for a more comprehensive assessment of syndromic conditions and the evaluation of CRC risk in patients' relatives. Panels routinely used in the U.S. (e.g., NCCN, Ambry Genetics®) include genes associated with: FAP (*APC*), MUTYH-associated polyposis (*MUTYH*), Peutz-Jeghers syndrome (*STK11*), juvenile polyposis (*BMPR1A*, *SMAD4*), Lynch syndrome (*MLH1, MSH2, MSH3, MSH6, PMS2, EPCAM*), polymerase proofreading-associated polyposis (*POLE, POLD1*), PTEN-related polyposis, and other genes whose association with familial or hereditary CRC has been confirmed in case-control studies (*AXIN2, ATM, GALNT12, CHEK2, GREM1, NTHL1*, and *TP53*). However, implementing such panels in Kazakhstan's oncology practice is limited, as the gene sets were designed for patient cohorts from the U.S., Europe, Southeast Asia, and China, whose ethnic-genetic backgrounds differ from those of the Kazakh population. It is known that some pathogenic variants exhibit ethnic and racial specificity in modulating CRC risk. Another limiting factor is the restricted scope of any diagnostic panel used for sequencing; in particular, the absence of clinically relevant genes such as *GSTM1, GSTT1, DCC*, and *RAS* in several commercial panels [50].

Conclusion: Over the past decade, multigene panels based on next-generation sequencing (NGS) have been introduced into both fundamental and practical oncology, enabling the analysis of multiple genes associated with specific HCS. This approach identifies variants in less well-studied gene regions and improves understanding of the mechanisms underlying predisposition to colorectal cancer (CRC), including early-onset disease. The NGS methodology enables the identification not only of pathogenic mutations but also of variants of uncertain functional significance, which may influence CRC predisposition. Variants in the *BRCA1, BRCA2, DICER1, FANCC, FANCM*, and *TSC2* genes, which alter protein function by disrupting critical cellular and tissue processes these genes regulate, expand the phenotypic spectrum of malignancies in CRC and help identify synchronous and metachronous neoplasms in other organs [50]. This personalizes treatment strategies for patients and enables early diagnosis and medical surveillance for their relatives.

References:

1. Mao R., Krautscheid P., Graham R.P., Ganguly A., Shankar S., Ferber M., Hegde M. Genetic testing for inherited colorectal cancer and polyposis, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG) // Genet. Med. – 2021. –Vol. 23(10). – P. 1807-1817. https://doi.org/10.1038/s41436-021-01207-9

2. Schubert S.A., Morreau H., de Miranda N.F.C.C., van Wezel T. The missing heritability of familial colorectal cancer // Mutagenesis. – 2019. – Vol. 35. – P. 221-231. https://doi.org/10.1093/mutage/gez027

3. Stoffel E., Koeppe E., Everett J., Ulintz P., Kiel M., Osborne J. Germline Genetic Features of Young Individuals with Colorectal Cancer // Gastroenterology. – 2018. – Vol. 154. – P. 897-905. https://doi.org/10.1016/j.physbeh.2017.03.040

4. Currais P., Rosa I., Claro I. Colorectal cancer carcinogenesis: From bench to bedside // World J Gastrointest Oncol. – 2022. – Vol. 14. – P. 654-663. https://doi.org/10.4251/wjgo.v14.i3.654

5. Zhunussova G., Afonin G., Abdikerim S., Jumanov A., Perfilyeva A., Kaidarova D., Djansugurova L. Mutation Spectrum of Cancer-Associated Genes in Patients With Early Onset of Colorectal Cancer // Front. Oncol. – 2019. – Vol. 9. – Art. no. 673. https://doi.org/10.3389/fonc.2019.00673

6. Tsaousis G.N., Papadopoulou E., Apessos A., Agiannitopoulos K., Pepe G., Kampouri S., Diamantopoulos N., Floros T., Iosifidou R., Katopodi O. Analysis of hereditary cancer syndromes by using a panel of genes: Novel and multiple pathogenic mutations // BMC Cancer. – 2019. – Vol. 19. – P. 535. https://doi.org/10.1186/s12885-019-5756-4

7. Tung N., Lin N.U., Kidd J., Allen B.A., Singh N., Wenstrup R.J., Hartman A.R., Winer E.P., Garber J.E. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients with Breast Cancer // J. Clin. Oncol. – 2016. – Vol. 34. – P. 1460-1468. https://doi.org/10.1200/JCO.2015.65.0747

8. Guindalini R.S.C., Viana D.V., Kitajima J.P.F.W., Rocha V.M., López R.V.M., Zheng Y., Freitas É., Monteiro F.P.M., Valim A., Schlesinger D., et al. Detection of germline variants in Brazilian breast cancer patients using multigene panel testing // Sci. Rep. – 2022. – Vol. 12. – Art. no. 4190. https://doi.org/org/10.1038/s41598-022-07383-1

9. Montalban G., Bonache S., Moles-Fernández A., Gisbert-Beamud A., Tenés A., Bach V., Carrasco E., López-Fernández A., Stjepanovic N., Balmana J. Screening of BRCA1/2 deep intronic regions by targeted gene sequencing identifies the first germline BRCA1 variant causing pseudoexon activation in a patient with breast/ovarian cancer // J. Med. Genet. – 2019. – Vol. 56. – P. 63-74. https://doi.org/10.1136/jmedgenet-2018-105606

10. Singh J., Thota N., Singh S., Padhi S., Mohan P., Deshwal S., Sur. S., Ghosh M., Agarwal A., Sarin R., et al. Screening of over 1000 Indian patients with breast and/or ovarian cancer with a multigene panel: Prevalence of BRCA1/2 and non-BRCA mutations // Breast Cancer Res. Treat. – 2018. – Vol. 170. – P. 189-196. https://doi.org/10.1007/s10549-018-4726-x

11. Bono M., Fanale D., Incorvaia L., Cancelliere D., Fiorino A., Calò V., Dimino A., Filorizzo C., Corsini L.R., Brando C. Impact of deleterious variants in other genes beyond BRCA1/2 detected in breast/ovarian and pancreatic cancer patients by NGS-based multigene panel testing: Looking over the hedge // ESMO Open. – 2021. – Vol. 6 (4). – Art. no. 100235. https://doi.org/10.1016/j.esmoop.2021.100235

12. Dámaso E., González-Acosta M., Vargas-Parra G., Navarro M., Balmana J., Ramon, Y., Cajal T., Tuset N., Thompson B.A., Marín F. Comprehensive Constitutional Genetic and Epigenetic Characterization of Lynch-Like Individuals // Cancers. – 2020. – Vol. 12. – Art. no. 1799. https://doi.org/10.3390/cancers12071799

13. Pearlman R., Frankel W.L., Swanson B., Zhao W., Yilmaz A., Miller K., Bacher J., Bigley C., Nelsen L., Goodfellow P.J. Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations

among Patients with Early-Onset Colorectal Cancer // JAMA Oncology. –2017. – Vol. 3. – P. 464-471. https://doi.org/10.1001/jamaoncol.2016.5194

14. Samadder N.J., Riegert-Johnson D., Boardman L., Rhodes D., Wick M., Okuno S. Comparison of universal genetic testing vs guideline-directed targeted testing for patients with hereditary cancer syndrome // JAMA Oncology. – 2021. – Vol. 7 (2). – P. 230-237. https://doi.org/10.1001/jamaoncol.2020.6252

15. Samadder N.J., Uson P.S., Riegert-Johnson D., Boardman L., Borad M., Ahn D. Germline cancer susceptibility gene testing in unselected patients with colorectal adenocarcinoma: A multi-center prospective study // Mol. Genet. Metabol. – 2021. – Vol. 132. – P. S34-S35. https://doi.org/10.1016/s1096-7192(21)00135-9

16. Liu X., Takata S., Ashikawa K., Aoi T., Kosugi S., Terao C., Parrish N.F., Matsuda K., Nakagawa H., Kamatani Y., Kubo M., Momozawa Y. Prevalence and Spectrum of Pathogenic Germline Variants in Japanese Patients With Early-Onset Colorectal, Breast, and Prostate Cancer // JCO Precis. Oncol. – 2020. – Vol. 4. – P. 183-191. https://doi.org/10.1200/PO.19.00224

17. Masson E., Zou W.B., Génin E., Cooper D.N., Le Gac G., Fichou Y., Pu N., Rebours V., Férec C., Liao Z., Chen J.M. Expanding ACMG variant classification guidelines into a general framework // Hum. Genom. – 2022. – Vol. 16(1). – Art. no. 31. https://doi.org/10.1186/s40246-022-00407-x

18. Bilyalov A., Danishevich A., Nikolaev S., Vorobyov N., Abramov I., Pismennaya E., Terehova S., Kosilova Y., Primak A., Stanoevich U., et al. Novel Pathogenic Variants in Hereditary Cancer Syndromes in a Highly Heterogeneous Cohort of Patients: Insights from Multigene Analysis // Cancers. – 2024. – Vol. 16(1). – Art. no. 85. http://dx.doi.org/10.3390/cancers16010085

19. Moller P., Seppala T.T., Bernstein I., Holinski-Feder E., Sala P., Gareth Evans D., Lindblom A., Macrae F., Blanco I., Sijmons R.H., et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: A report from the Prospective Lynch Syndrome Database // Gut. – 2018. – Vol. 67. – P. 1306-1316. https://doi.org/10.1136/gutjnl-2017-314057

20. Gray P. N., Tsai P., Chen D., Wu S., Hoo J., Mu W., Li B., Vuong H., Lu H., Batth N., Willett S., Uyeda L., Shah S., Terdiman J. TumorNext-Lynch-MMR: a comprehensive next generation sequencing assay for the detection of germline and somatic mutations in genes associated with mismatch repair deficiency and Lynch syndrome // Oncotarget. – 2018. – Vol. 9. – P. 20304-20322. https://doi.org/10.18632/oncotarget.24854

21. Liu H.X., Zhou X.L., Liu T., Werelius B., Lindmark G., Dahl N., Lindblom A. The role of hMLH3 in familial colorectal cancer // Cancer Res. – 2003. – Vol. 63. – P. 1894-1899. https://pubmed.ncbi.nlm.nih.gov/12702580/

22. Djursby M., Madsen M.B., Frederiksen J.H., Berchtold L.A., Therkildsen C., Willemoe G.L., Hasselby J.P., Wikman F., Okkels H., Skytte A.-B., Nilbert M., Wadt K., Gerdes A.-M., van Overeem Hansen T. New Pathogenic Germline Variants in Very Early Onset and Familial Colorectal Cancer Patients // Front. Genet. – 2020. – Vol. 11. – Art. no. 566266. https://doi.org/10.3389/fgene.2020.566266

23. Okkels H., Lagerstedt-Robinsson K., Wikman F.P., Hansen T.O., Lolas I., Lindberg L.J. Detection of PMS2 mutations by screening hereditary nonpolyposis colon cancer families from Denmark and Sweden // Genet. Test. Mol. Biomarker. – 2019. – Vol. 23. – P. 688-695. https://doi.org/10.1089/gtmb.2018.0316

24. Houlleberghs H., Dekker M., Lantermans H., Kleinendorst R., Dubbink H. J., Hofstra R. M. W. Oligonucleotide-directed mutagenesis screen to identify pathogenic Lynch syndrome-associated MSH2 DNA mismatch repair gene variants // Proc. Natl. Acad. Sci. US. – 2016. – Vol. 113. – P. 4128-4133. https://doi.org/10.1073/pnas.1520813113

25. Rath A., Mishra A., Ferreira V. D., Hu C., Omerza G., Kelly K., Hesse A., Reddi H.V., Grady J.P., Heinen C.D. Functional interrogation of Lynch syndrome-associated MSH2 missense variants via CRISPR-Cas9 gene editing in human embryonic stem cells // Hum. Mutat. – 2019. – Vol. 40. – P. 2044-2056. https://doi.org/10.1002/humu.23848

26. Guda K., Moinova H., He J., Jamison O., Ravi L., Natale L., Lutterbaugh J., Lawrence E., Lewis S., Willson J.K. Inactivating germline and somatic mutations in polypeptide N-acetylgalactosaminyltransferase 12 in human colon cancers // Proc. Natl. Acad. Sci. U.S.A. – 2009. – Vol. 106. – P. 12921-12925. https://doi.org/10.1073/pnas.0901454106

27. Evans D.R., Venkitachalam S., Revoredo L., Dohey A.T., Clarke E., Pennell J.J., Powell A.E., Quinn E., Ravi L., Gerken T.A., Green J.S., Woods M.O., Guda K. Evidence for GALNT12 as a moderate penetrance gene for colorectal cancer // Hum. Mutat. – 2018. – Vol. 39. – P. 1092-1101. https://doi.org/10.1002/humu.23549

28. Wang D., Zhang Z., Li Y., Xu C., Yu Y., Li M. Adenomatous polyposis coli gene mutations in 22 Chinese pedigrees with familial adenomatous polyposis // Med. Sci. Monit. – 2019. – Vol. 25. – P. 3796-3803. https://doi.org/10.12659/MSM.913911

29. Short E., Thomas L.E., Hurley J., Sian J., Sampson J.R. Inherited predisposition to colorectal cancer: towards a more complete picture // J. Med. Genet. – 2015. – Vol. 52 (12). – P. 791-796. https://doi.org/10.1136/jmedgenet-2015-103298

30. Thiffault I., Saunders C., Jenkins J., Raje N., Canty K., Sharma M., Grote L., Welsh H.I., Farrow E., Twist G. A patient with polymerase E1 deficiency (POLE1): Clinical features and overlap with DNA breakage/instability syndromes // BMC Med. Genet. – 2015. – Vol. 16. – Art. no. 31. https://doi.org/10.1186/s12881-015-0177-y

31. Logan C.V., Murray J.E., Parry D.A., Robertson A., Bellelli R., Tarnauskaite Ž., Challis R., Cleal L., Borel V., Fluteau A. et al. DNA Polymerase Epsilon Deficiency Causes IMAGe Syndrome with Variable Immunodeficiency // Am. J. Hum. Genet. – 2018. – Vol. 103. – P. 1038-1044. https://doi.org/10.1016/j.ajhg.2018.10.024

32. Mur P., García-Mulero S., Del Valle J., Magraner-Pardo L., Vidal A., Pineda M., Cinnirella G., Martín-Ramos E., Pons T., López-Doriga A. Role of POLE and POLD1 in familial cancer // Genet. Med. – 2020. – Vol. 22. – P. 2089-2100. https://doi.org/10.1038/s41436-020-0922-2

33. Elsayed F.A., Kets C.M., Ruano D., van den Akker B., Mensenkamp A.R., Schrumpf M., Nielsen M., Wijnen J.T., Tops C.M., Ligtenberg, M.J. Germline variants in POLE are associated with early onset mismatch repair deficient colorectal cancer // Eur. J. Hum. Genet. – 2015. – Vol. 23. – P. 1080-1084. https://doi.org/10.1038/ejhg.2014.242

34. Hansen M.F., Johansen J., Sylvander A.E., Bjørnevoll I., Talseth-Palmer B.A., Lavik L.A.S., Xavier A., Engebretsen L.F., Scott R.J., Drabløs F., Sjursen W. Use of multigene-panel identifies pathogenic variants in several CRC-predisposing genes in patients previously tested for Lynch Syndrome // Clin. Genet. – 2017. – Vol. 92(4). – P. 405-414. https://doi.org/10.1111/cge.12994

35. Rohlin A., Zagoras T., Nilsson S., Lundstam U., Wahlström J., Hultén L., et al. A mutation in POLE predisposing to a multi-tumour phenotype // Int. J. Oncol. – 2014. – Vol. 45. – P. 77-81. https://doi.org/10.3892/ijo.2014.2410

36. Vande Perre P., Siegfried A., Corsini C., Bonnet D., Toulas C., Hamzaoui N., et al. Germline mutation p.N363K in POLE is associated with an increased risk of colorectal cancer and giant cell glioblastoma // Fam. Cancer. – 2019. – Vol. 18. – P. 173-178. https://doi.org/10.1007/s10689-018-0102-6

37. Bellido F., Pineda M., Aiza G., Valdés-Mas R., Navarro M., Puente D. A. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance // Genet. Med. – 2016. – Vol. 18. – P. 325-332. https://doi.org/10.1038/gim.2015.75

38. Choi M., Kipps T., Kurzrock R. ATM Mutations in Cancer: Therapeutic Implications // Mol. Cancer Ther. – 2016. – Vol. 15. – P. 1781-1791. https://doi.org/10.1158/1535-7163.MCT-15-0945

39. Costa H.A., Leitner M.G., Sos M.L. Discovery and functional characterization of a neomorphic PTEN mutation // Proc. Natl. Acad. Sci. U.S.A. – 2015. – Vol. 112. – P. 13976-13981. https://doi.org/10.1073/pnas.1422504112

40. Talseth-Palmer B. A., Bauer D. C., Sjursen W., Evans T. J., Mcphillips M., Proietto A. Targeted next-generation sequencing of 22 mismatch repair genes identifies Lynch syndrome families // Cancer Med. – 2016. – Vol. 5. – P. 929-941. https://doi.org/10.1002/cam4.628

41. Weren R. D. A., Ligtenberg M. J. L., Kets C. M., De Voer R. M., Verwiel E. T. P., Spruijt L. A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer // Nat. Genet. – 2015. – Vol. 47. – P. 668-671. https://doi.org/10.1038/ng.3287

42. Adam R., Spier I., Zhao B., Kloth M., Marquez J., Hinrichsen I., et al. Exome sequencing identifies biallelic Msh3 germline mutations as a recessive subtype of colorectal adenomatous polyposis // Am. J. Hum. Genet. – 2016. – Vol. 99. – P. 337-351. https://doi.org/10.1016/j.ajhg.2016.06.015

43. Valle L., de Voer R.M., Goldberg Y., Sjursen W., Försti A., Ruiz-Ponte C., et al. Update on genetic predisposition to colorectal cancer and polyposis // Mol Aspects Med. – 2019. – Vol. 69. – P. 10-26. https://doi.org/10.1016/j.mam.2019.03.001

44. te Paske I.B.A.W., Ligtenberg M.J.L., Hoogerbrugge N., de Voer R.M. Candidate Gene Discovery in Hereditary Colorectal Cancer and Polyposis Syndromes – Considerations for Future Studies // Int J Mol Sci. – 2020. – Vol. 21(22). – P. 8757. http://dx.doi.org/10.3390/ijms21228757

45. Fernandez-Rozadilla C., Alvarez-Barona M., Quintana I., Lopez-Novo A., Amigo J., Cameselle-Teijeiro J.M. Exome sequencing of early-onset patients supports genetic heterogeneity in colorectal cancer // Sci. Rep. – 2021. – Vol. 11(1). – P. 1-9. https://doi.org/10.1038/s41598-021-90590-z

46. Fabišikova K., Hamidova O., Behulova R.L., Zavodna K., Priščakova P., Repiska V. Case Report: The Role of Molecular Analysis of the MUTYH Gene in Asymptomatic Individuals // Front. Genet. – 2020. – Vol. 11. – Art. no. 590486. http://dx.doi.org/10.3389/fgene.2020.590486

47. Fahed A.C., Wang M., Homburger J.R., Patel A.P., Bick A.G., Neben C.L. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions // Nat. Commun. – 2020. – Vol. 11(1). – P. 1-9. https://doi.org/10.1038/s41467-020-17374-3

48. Karczewski K.J., Francioli L.C., Tiao G., Cummings B.B., Alfoldi J., Wang Q. The mutational constraint spectrum quantified from variation in 141,456 humans // Nature. – 2020. – Vol. 581(7809). – P. 434-43. https://doi.org/10.1038/s41586-020-2308-7

49. Afonin G.A., Baltayev N.A., Kaidarova D.R., Ababakriev A.K., Kalmenova P.B. Clinical and phenotypic variants of hereditary and sporadic colorectal cancer in young patients // Oncol. Radiol. Kazakhstan. – 2021. – Vol. 2 (60). – P. 9-21. https://elibrary.ru/download/elibrary_48037351_19835183.pdf

50. Afonin G.A. Molekulyarno-geneticheskij analiz razvitiya kolorektal'nogo raka u bol'nyx v vozraste do 50 let: dis. … dok. filosofii: 6 D110100. – Almaty: KazNMU im. S.D. Asfendiyarova, 2022. – 220 s. [50. Afonin G.A. Molecular genetic analysis of colorectal cancer development in patients under 50 years of age: PhD thesis in 6 D110100. – Almaty: Asfendiyarov KazNMU, 2022. – 220 p. (in Russ.)]. https://kaznmu.edu.kz/wp-content/uploads/2024/10/Диссертация-Афонина-Г.А.pdf

51. Kuzbari Z., Bandlamudi C., Loveday C., Garrett A., Mehine M., George A., Hanson H., Snape K., Kulkarni A., Allen S., Jezdic S., Ferrandino R., Westphalen C.B., Castro E., Rodon J., Mateo J., Burghel G.J., Berger M.F., Mandelker D., Turnbull C. Germline-focused analysis of tumour-detected variants in 49,264 cancer patients: ESMO Precision Medicine Working Group recommendations // Ann. Oncol. – 2023. – Vol. 34(3). – P. 215-227. https://doi.org/10.1016/j.annonc.2022.12.003

АҢДАТПА

ТҰҚЫМ ҚУАЛАЙТЫН ЖӘНЕ СПОРАДИКАЛЫҚ КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІКТІҢ ГЕНЕТИКАЛЫҚ СКРИНИНГІНДЕГІ МУЛЬТИГЕНДІК ТЕСТІЛЕУ: ӘДЕБИЕТКЕ ШОЛУ

Н.А. Балтаев[1], Г.А. Афонин[1,2], Г.С. Жунусова[3], Д.Р. Кайдарова[2], В.Ю. Белоусов[4]

[1]«Алматы онкологиялық орталығы» ШЖҚ КМК, Алматы, Қазақстан Республикасы;
[2]«С.Ж. Асфендияров атындағы Қазақ ұлттық медицина университеті» КЕАҚ, Алматы, Қазақстан Республикасы;
[3]Қазақстан Республикасы Ғылым және жоғары білім министрлігі Ғылым комитетінің Генетика және физиология институты ШЖҚ РМК, Алматы, Қазақстан Республикасы;
[4]«Tree Gene генетикалық зертханасы» ЖШС, Алматы, Қазақстан Республикасы

Өзектілігі: *Науқастың генотипін және ісіктің молекулалық профилін анықтауға арналған молекулалық-генетикалық тестілеу емдеуге және клиникалық тексеруге дербестендірілген тәсілдің негізгі құрамдас бөлігі болып табылады. Генетикалық скринингтегі қазіргі зерттеулер фенотиптік диагностикалық панельдерден және сезімталдық гендерін ПТР тестілеуден көптеген анықталған гендерді немесе тұтас геном секвенциясын қамтитын үлкен панельдерге өтуге бағытталған. Мультигендік тестілеу колоректальды қатерлі ісік (КҚІ) диагностикасы мен терапиясының әртүрлі салаларында кеңінен қолданылады, оның пайда болуына генетикалық компоненттер маңызды үлес қосады. Қазіргі уақытта практикалық онкология КҚІ тұқым қуалайтын және спорадикалық нұсқаларының генетикалық скринингі үшін жоғары өнімді секвенирлеу жүйелерін қайта қарауды және пациенттердің туыстарында оның ерте диагностикасын оңтайландыруды талап етеді.*

Зерттеудің мақсаты *– тұқым қуалайтын және спорадикалық колоректальды обырдың генетикалық скринингі үшін келесі буынды секвенирлеуді (NGS) қолданудың әдіснамасы мен ағымдағы нәтижелеріне шолу.*

Әдістері: *Google Scholar, Web of Science, Springer Link, Scopus, Science Direct, PubMed, BMJ сайттарында ашық қолжетімділікте қолжетімді түпнұсқалық зерттеулер мен шолу мақалаларын қоса алғанда, 70 ғылыми жарияланымға аналитикалық шолу жүргізілді.*

Нәтижелері: *NGS негізіндегі мультигенді тестілеу канцерогенезге қатысатын бірнеше гендерді бір уақытта талдауға мүмкіндік береді, тұқым қуалайтын қатерлі ісік синдромдарымен байланысты патогенді ұрық сызығының мутацияларын, сондай-ақ интрондық және трансляцияланбаған аймақтар сияқты гендердің нашар түсінілген аймақтарындағы генетикалық нұсқаларды анықтауға мүмкіндік береді, бұл КҚІ қоздыратын бұрын белгісіз факторларды анықтауға көмектеседі.*

Қорытынды: *Молекулярлық-генетикалық диагностика пациенттерді жеке емдеуге және тәуекел топтарындағы туыстарды жеке медициналық тексеруге мүмкіндік береді. Дегенмен, КҚІ жағдайларының шамамен 25% отбасылық болса да, отбасылардың шамамен 95% генетикалық сынақтан өтпеген. Талданған деректер тұқым қуалайтын ісік синдромдарына немесе тұтас геномды секвенирлеуге қатысатын барлық анықталған гендерді қоса алғанда, фенотиптік панельдерден үлкен*

панельдерге көшу қажеттілігін қолдайды. Сонымен қатар, орташа және төмен еніп кететін жаңа нұсқаларды немесе функционалдық мәні белгісіз нұсқаларды анықтау ККІ фенотиптік спектрін кеңейтеді және диагностикалық секвенирлеу панельдеріне қосу үшін осы нұсқаларды әрі қарай зерттеуді қажет етеді.

Түйінді сөздер: *Колоректальды қатерлі ісік (ККІ), патогендік мутациялар, келесі ұрпақ секвенирлеу, тұқым қуалайтын тұқым қуалайтын тоқ ішек қатерлі ісігі, генетикалық скрининг.*

АННОТАЦИЯ

МУЛЬТИГЕННОЕ ТЕСТИРОВАНИЕ В ГЕНЕТИЧЕСКОМ СКРИНИНГЕ НАСЛЕДСТВЕННОГО И СПОРАДИЧЕСКОГО КОЛОРЕКТАЛЬНОГО РАКА: ОБЗОР ЛИТЕРАТУРЫ

Н.А. Балтаев[1], Г.А. Афонин[1,2], Г.С. Жунусова[3], Д.Р. Кайдарова[2], В.Ю. Белоусов[4]

[1]ГКП на ПХВ «Алматинский онкологический центр», Алматы, Республика Казахстан;
[2]НАО «Казахский национальный медицинский университет им. С.Д. Асфендиярова», Алматы, Республика Казахстан;
[3]РГП на ПХВ «Институт генетики и физиологии» Комитета науки МНВО РК, Алматы, Республика Казахстан;
[4]ТОО «Генетическая лаборатория Tree Gene», Алматы, Республика Казахстан

Актуальность: *Молекулярно-генетическое тестирование для определения генотипа пациента и молекулярного профиля опухоли представляет собой ключевой компонент персонализированного подхода к лечению и диспансеризации. Современные исследования в области генетического скрининга фокусируются на переходе от диагностических панелей, основывающихся на фенотипе, и ПЦР-тестирования отдельных генов предрасположенности к большим панелям или полногеномному секвенированию. Мультигенное тестирование находит широкое применение в различных областях диагностики и терапии колоректального рака (КРР), в возникновении которого значителен вклад генетических компонентов. В настоящее время в практической онкологии необходим обзор систем высокопроизводительного секвенирования для генетического скрининга наследственных и спорадических вариантов КРР и оптимизации его ранней диагностики у родственников пациентов.*

Цель исследования *– обзор методологии и современных результатов применения секвенирования нового поколения (NGS) для генетического скрининга наследственного и спорадического колоректального рака.*

Методы: *Проведен аналитический обзор 114 научных публикаций, включая оригинальные исследования и обзорные статьи, находящихся в открытом доступе в Google Scholar, Web of Science, Springer Link, Scopus, Science Direct, PubMed, BMJ.*

Результаты: *Мультигенное тестирование на основе NGS позволяет проводить одновременный анализ множества генов, участвующих в канцерогенезе, идентифицировать герминальные патогенные мутации, ассоциированные с наследственными опухолевыми синдромами, а также генетические варианты в менее изученных областях генов, таких как интронные и нетранслируемые области, что способствует выявлению ранее неизвестных факторов предрасположенности к КРР и оценке их вклада в реализацию опухолевого процесса.*

Заключение: *Молекулярно-генетическая диагностика делает возможным персонализированное лечение пациентов и индивидуализированную диспансеризацию родственников из групп риска. Однако несмотря на то, что около 25% случаев КРР являются семейными, около 95% семей остаются генетически не исследованы. Проанализированные данные подтверждают необходимость перехода от панелей, основанных на фенотипе к большим панелям, включающим все идентифицированные гены, вовлеченные в наследственные опухолевые синдромы или секвенирование всего генома. Кроме того, идентификация новых вариантов с умеренной и низкой пенетрантностью или вариантов с неопределенным функциональным значением, обладающих патогенным эффектом по данным in silico анализа, расширяет фенотипический спектр КРР, и обусловливает необходимость дальнейших исследований этих вариантов для включения в диагностические панели.*

Ключевые слова: *колоректальный рак (КРР), патогенные мутации, секвенирование нового поколения (NGS), наследственный рак толстой кишки, генетический скрининг.*

Transparency of the study: *Authors take full responsibility for the content of this manuscript.*
Conflict of Interests: *The authors declare no conflict of interest.*
Funding: *The authors declare no funding for the study.*
Authors Contribution: *Conceptualization, Investigation – G.A. Afonin, N.A. Baltayev; Study Design – G.A. Afonin, D.R. Kaidarova, G.S. Zhunusova; Validation – G.A. Afonin, G.S. Zhunusova, V.Yu. Belousov; Writing – Original Draft Preparation – all authors.*
Information about the Authors:
N.A. Baltayev (Corresponding author) – Head of the Department of Oncology, Almaty Oncology Center, Almaty, Kazakhstan, tel. +77017992353, email: nurlan.baltayev@mail.ru, ORCID: 0000-0003-3022-7372;
G.A. Afonin – PhD, Associate Professor, the Department of Oncology, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan, +77017838196, email: ilyenkov_diamat@mail.ru, ORCID: 0000-0001-9314-6938;
G.S. Zhunusova – PhD, Leading Researcher at the Laboratory of Molecular Genetics, Institute of Genetics and Physiology, Ministry of Science and Higher Education, Almaty, Kazakhstan, tel. +77471035214, email: gulnur_j@mail.ru, ORCID: 0000-0001-8642-9577;
D.R. Kaidarova – Doctor of Medical Sciences, Professor, Academician of the NAS RK, Head of the Department of Oncology, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan, +77017116593, email: dilyara.kaidarova@gmail.com, ORCID: 0000-0002-0969-5983;
V.Yu. Belousov – Candidate of Biology, Director of Tree Gene genetic laboratory, Almaty, Kazakhstan, tel. +77776567655, email: beloussov@tree-gene.com, ORCID: 0000-0003-1922-156X.

Address for Correspondence: N.A. Baltayev, Almaty Oncology Center, Papanin St. 220a, Almaty 050054, Kazakhstan.