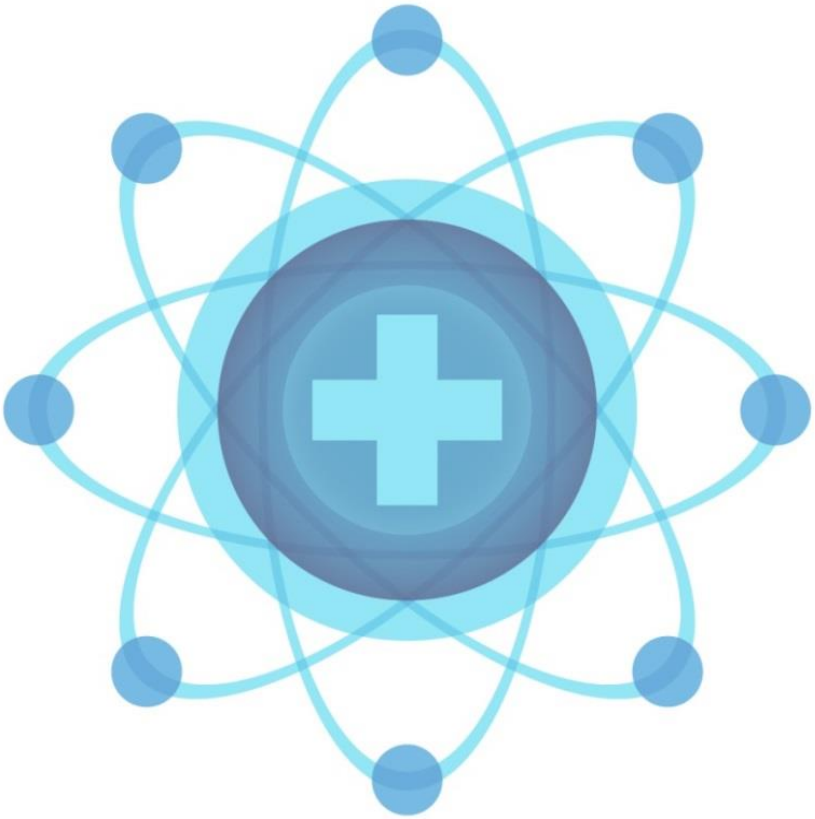

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INDIVIDUAL PREDISPOSITION IN THE ORIGIN OF COLORECTAL CANCER, HEREDITARY AND ACQUIRED CANCER, THE IMPORTANCE OF HUMAN GENETIC STRUCTURE IN THE DEVELOPMENT OF CANCER, GENE AND CHROMOSOMAL MUTATIONS

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Abstract: Understanding the molecular basis of individual susceptibility to colorectal cancer and the factors involved in the development of the tumor, prevention of tumor development, methods of early detection of the development of colon cancer in people with a genetic predisposition and practical application of these methods.

Keywords: genetic instability, Chromosomal mutation, HNPPC, lynch syndrome, TP53 genetic test.

Introduction. In the United States, about 160,000 people are diagnosed with colon cancer each year, and 57,000 patients die from the disease, making it the second leading cause of cancer death among adults [1]. Cancer often begins as an adenomatous polyp, and in many cases, malignancy occurs, resulting in a high-grade dysplastic adenoma and then invasive cancer. Invasive cancers located in the colon wall (in stages I and II of the cancer) is treated, but if left untreated, the organism spreads by lymph flow and blood flow (lymphogenic and hematogenous way). Oncogenic cells spread through hematogenous and lymphogenic ways and give distant metastases (stage III-IV). In stages I and II (depending on the layer to which the tumor has penetrated through the invasive way), surgical treatment of the tumor is carried out, and in up to 73% of cases of stage III diseases, adjuvant chemotherapy, combined with radiation therapy treated with surgery [1].

The latest achievements in the field of chemotherapy increase the possibility of prolonging human life, but in the IV stage of the disease, the scope of radiation therapy and chemotherapy treatment is small. Genetic instability (confusion of certain parts of the genome) in the human body causes various mutations in the body, and these conditions often lead to the development of various cancers, including colorectal cancer. Chromosome and DNA instability, which are common types of genetic instability, often lead to the development of colorectal cancer. Chromosome instability, that is, confusion in the chromosome, causes many mutations in the number and structure of chromosome copies. When the genetics of some groups of people with colon cancer are studied, they have mutations in the DNA mismatch repair system. The incidence of colon cancer has increased. These genetic changes are passed down from generation to generation, creating a genetic predisposition. If family members are affected by cancer, the affected person should undergo genetic tests, and in cases where a genetic mutation is detected, these family members are

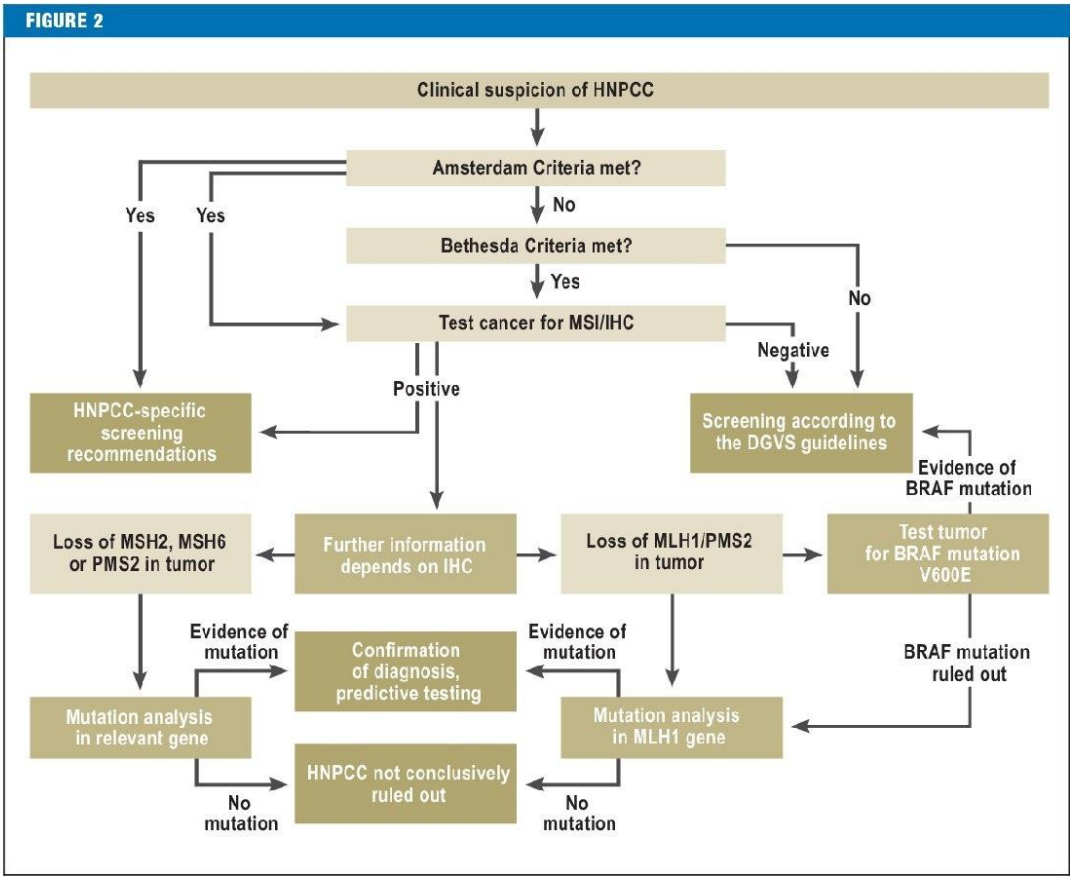
considered to be in the risk group, and every year, a modern, convenient screening method such as Fobt, iFobt it is recommended to retain the inspection methods [2]

If a positive result is obtained in this screening method, a colonoscopy examination method is used based on a referral and is taken under the control of an oncologist. In addition to genetic predisposition, cancer can be non-hereditary, i.e. acquired during a person's life, i.e. there are also non-hereditary cases [3].

iHNPCC - Hereditary Nonpolyposis Colorectal Cancer (Lynch syndrome) is an autosomal dominant disease. This syndrome is caused by a mutation in one of the four genes in the DNA mismatch repair system. Its prevalence in the general population is about 1 in 500 [4]. Lynch syndrome is suspected if unusual cancer symptoms are observed early in the patient (that is, if the patient develops cancer at an early age, that is, before the age of 45, or if there are people with cancer due to genetic instability in the family cluster, that is, microsatellite instability, protein mutations that correct genetic instability are observed) If this is found, the patient will be examined further and the genetic mutation will be sought. In various genetic diseases, it is recommended to diagnose patients with a pathogenic mutation and identify other family members. Mutations occur in genes that restore the imbalance in HNPCC patients. The MLH1 and MSH2 genes, which are part of the MMR gene set, are considered to be genes that store information on the production of a protein that is important in the repair of mutations in DNA. The protein produced by this information is PMS2. It combines with the PMS2 protein formed by gene activation to form a dimer protein complex, and this protein complex is considered one of the factors that regulate the imbalance of errors in DNA replication. As a result of mutation of the MLH1 MSH2 genes, the risk of colon and rectal cancer in the body is 52-82%. will be in percentages. Germline defects account for approximately 80% of the lifetime risk of colon cancer, and the cancer does not appear until the average age of 45. Loss of mismatch repair function in HNPCC patients depends not only on the mutant germ-line and mismatch repair gene, but also on somatic inactivation of the parental allele. Cancer progression is accelerated in patients with HNPCC. Germ-line mutations in another mismatch repair gene, MSH6, reduce susceptibility to familial cancer. Somatic inactivation of genetic imbalance genes occurs in approximately 15% of patients with HNPCC. The loss of imbalance repair can be detected by the epiphenomenon of microsatellite instability, in which the impossibility of slippage and entanglement of strands due to repetitive DNA sequence measures changes the size of mononucleotides or dinucleotides (microsatellites). It is possible to produce products with components or restore the imbalance in the absence of one. Polyposis is considered to be a major regenerative factor in non-hereditary cancer, and in many cases, these polyposis are caused by the effects of intestinal peristalsis and digested food mass, as well as other harmful effects. Cancer is the result of malignancy. 15% or more of people who develop colorectal adenomas have MYH-related polyposis.

This creates common genetic diseases, (multiple mutations contribute to diseases, (multiple mutations contribute to diseases) and G382D genes), which creates common genetic diseases. There are many common mechanisms in the occurrence of colorectal: genes, various mutations in receptors, disruption of physiological processes. These processes cause the development of cancer.

Algorithms for the diagnosis of HNPCC
HNPCC, hereditary nonpolyposis colorectal cancer; DGVS, German Society for Digestive and Metabolic Disorders; MSI, microsatellite instability; IHC, immunohistochemistry



When HNPCC syndrome is suspected, a family cluster is studied and genetic screening tests are performed as described above. In most cases, cancer develops as a result of mutations caused by an imbalance in genes such as MSH2 and MSH6 [5-7].

Oncotests such as MSI/HC are available to detect this process. If a positive result is obtained from this test, in-depth investigations are carried out, MLH1 oncotest is performed, this test determines the presence of the mutation process.

Epigenetic blocking of genes often associated with aberrant DNA methylation is thought to be a mechanism of gene inactivation in patients with solid cancer. Aberrant DNA methylation is one of the important processes in the development of colorectal cancer. Initially, this process was studied in the early 1980s, but due to the lack of certain accuracy, many researches were conducted and later convenient [8]. A more complex PCR (MPS) method was developed. The MSP method is a method aimed at detecting only methylated or unmethylated bases. It is a method based on comparing the ratio of methylated and unmethylated PCR products to measure very low levels of methylation at specific loci. In a normal genome, cytosine methylation occurs in regions of DNA sequence repeats outside of exons. Due to confusion, under

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the influence of oxygen, arginine is attached to guanine instead of cytosine, and in normal conditions, guanine forms a bond with cytosine. this imbalance is resolved by MYH glycolidase. But the means of production can be monitored and special productions come, these mutations multiply several indicators of cancer transformation structures and special CpG islands are also present. In comparison, a global reduction in cytosine methylation was observed in the colorectal cancer genome, within CpG islands associated with promoters with increased levels of abnormal methylation. The CpG island promoter is considered part of the gene inactivation mechanism in cancer. Methylation associated with this aberrant promoter can lead to epigenetic blocking of gene expression. As can be seen from these processes, the importance of the methylation process in colorectal cancer is great. Another factor, P53, is a transcription factor that regulates the cell cycle, and this factor mediates disease production. Therefore, the 3 gene is one of the anti-oncogene TP5 genes [9]. Mutations in the TP53 gene occur in 50% of cases during the development of cancer. Inactivation of the p53 pathway by TP53 mutation is the main development of colorectal cancer. In many tumors, two TP53 alleles are inactivated by mutation of inactive programs and deletion of the TP53 allele in combination with chromosome 17p deletion [10]. Mutational inactivation of TGF-β signaling is the regulation of the physiological processes of the growth factor TGF-β, while having significant damage in the control of proliferation, differentiation and angiogenesis processes. The TGFBR2 gene is under the control of type 2 growth factor TGF-β. gives information about. In one-third of colorectal cancers, somatic mutations inactivate TGFBR2 and mediate colorectal cancer progression. Another important source is mitogen-activated protein kinase. This factor regulates cell functions such as proliferation, gene expression, differentiation, mitosis, cell protection, apoptosis, and at the same time participates in regulating the release of regenerative cytokines [12].

Oncogenic mutations of reticular signaling systems (RAS) and BRAF, which activate the MAPK signaling pathway, are present in 37% and 13% of colon cancer patients. 21,55,57,70,71 RAS mutations play an important role in the development of colorectal cancer. BRAF mutations indicate BRAF serine-threonine kinase activity, which further regulates MAPK signaling 70,71 BRAF mutations occur even in small polyps21 and compared to RAS mutations, they are more common in hyperplastic polyps, serrated adenomas, and proximal colon especially common in colon cancer. People with CIMP (CpG island methylator phenotype). In patients with multiple hyperplastic diseases diagnosed with hyperplastic polyposis syndrome, colon disease is carried out through an intermediate lesion with a jagged luminal border. One-third of colorectal cancer is phosphatidylinositol. Active behavior involves somatic mutations of PI3KCA, which encodes the catalytic subunit of kinase 3 (PI3K). 72 Less common genetic alterations that replace PI3KCA mutations include loss of

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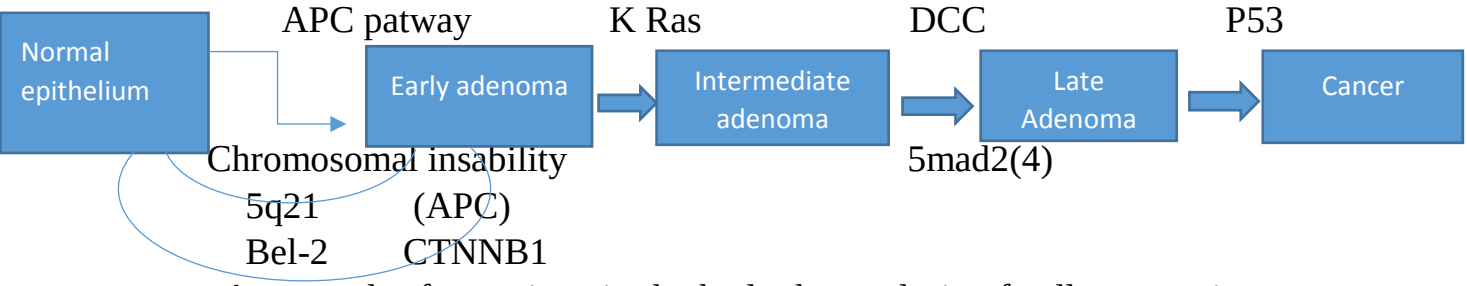
PTEN, an inhibitor of PI3K signaling. PTEN catalyzes the cleavage of the phosphate group of the inositol ring of phosphatidylinositol 3-phosphate. It activates coamplification of insulin receptor substrate 2 (IRS2), an upstream activator of PI3K signaling, and AKT and PAK4, downstream mediators of PI3K signaling. PTEN catalyzes the cleavage of the phosphate group of the phosphatidylinositol 3-phosphate inositol ring. It activates insulin receptor substrate 2 (IRS2), an upstream activator of PI3K signaling, and coamplification of AKT and PAK4, downstream mediators of PI3K signaling. According to the National Center for Biotechnology Information Reference Sequence (RefSeq). Somatic mutations were detected in 848 genes in people with colorectal cancer [12]. As originally developed, the adenoma-to-carcinoma transition sequence 2,28,43 is a model of colorectal cancer development in which specific tumor-promoting mutations occur stepwise. This model refers to the presence of mutations that indicate specific characteristics of the tumor, such as the presence of nearby or distant metastases. It is important to study the results of whole genome sequencing of primary colon cancer and distant metastases in the patient. In this case, we can observe new mutations in metastases. An early and important step in the development of adenoma is the activation of prostaglandin signaling. can occur due to regulation. E2, an agent strongly associated with colon cancer. Prostaglandin E2 activity can also be increased by loss of 15-prostaglandin dehydrogenase (15-PGDH), the rate-limiting enzyme that catalyzes prostaglandin degradation [13].

This condition occurs in approximately two-thirds of colorectal cancers, and 15-PGDH is lost in 80% of colon adenomas and cancers. In humans, the incidence and mortality rate of CRC has been observed to be low. Selective cyclooxygenase enzymes are required for the conversion of arachidonic acid to prostaglandins. COX 1-COX2 plays an important role in the development of colorectal cancer, and this factor mediates the development of adenomas and the regression of existing adenomas. The next factor is epidermal growth factor (EGF), a soluble protein that naturally has a trophic effect on intestinal cells. According to the results of clinical studies, an important signaling pathway is stimulated by the EGF receptor (EGFR) in a subgroup of colorectal cancers. EGFR mediates signaling by activating the MAPK and PI3K signaling cascades. Recent clinical data showed that advanced colon cancer with tumorigenic mutations of these pathways, including KRAS,92-94 BRAF,95,96 and PI3K97 p110 s activating mutations, is unresponsive to anti-EGFR therapy [14]. Vascular endothelial growth factor (VEGF), produced during injury or normal tissue growth, stimulates the production of new stromal blood vessels (angiogenesis). Clinical studies have shown that the role of angiogenic pathways is also important in the growth and death of colorectal cancer. Treatment with anti-VEGF prolonged the overall survival of colon cancer patients by an average of 4.7 months (15.6 months with standard therapy).

Normal stem cells located in colonic crypts rely on adhesive and soluble stromal-epithelial factor to maintain division and differentiation. Changes in these regulatory mechanisms in colorectal cancer stem cells are a promising area of research, as agents that control the growth of colorectal cancer stem cells could theoretically be used for cancer prevention and treatment. EGFR signaling components RAS and BRAF mutations and anti-EGFR therapy the relationship between the current is one of the only measures in the treatment of colorectal cancer genomics. Several genomic markers are useful for prognosis. For example, germ-line mutations in genes that mediate genetic instability, such as APC, MLH1, and MSH2, are associated with a significantly increased risk of colorectal cancer. The development of molecular diagnostics for early detection of colorectal cancer is of great importance for the in-depth study of the genetics of colon cancer in clinical practice. One example is the development of assays to detect mutations specific to colon cancer and cancer-related aberrant DNA methylation in stool DNA from patients with colon cancer or advanced adenomas. These tests have a sensitivity of 46 to 77% for detecting colon cancer at an early stage, which is superior to the sensitivity of fecal occult blood tests, but their superiority in preventing death from cancer has not been shown. Colorectal cancer DNA testing has been added to the American Cancer Society's cancer screening guidelines and is highly sensitive for detecting advanced adenomas. Detecting colorectal cancer at the cellular level will greatly improve the survival and work capacity of people with cancer [15].



As a result of mutations in the body, hyperplasia of cells occurs in many cases, as a result of which adenomas appear, there are factors that affect this, and as a result of these effects, tumors of poor quality appear.

Conclusion. In conclusion, a deep study of colorectal cancer at the gene level and the establishment of effective screening procedures for people with a genetic predisposition will prevent the development of this disease, identify the cause of the disease in people with colorectal cancer, and correct It is important to carry out treatment today. For this, it is necessary to develop and implement screening programs that are perfectly minimally invasive.

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