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THERAPEUTIC APPROACHES TO RESTORING THE ANTIATHEROGENIC FUNCTION OF HIGH DENSITY LIPOPROTEINS

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A low level of high density lipoproteins (HDLs) in blood plasma is considered to be an important risk factor for the development of atherosclerosis. The antiatherogenic function of HDLs is associated with their participation in the reverse transport of excess cholesterol from peripheral tissues to the liver. In addition, they have antioxidant, anti-inflammatory, antithrombotic and anti-infectious properties, which also contribute to their atheroprotective effect. Recent studies have shown that the structure and composition of HDLs can change under various pathological conditions, thus leading to the appearance of dysfunctional HDLs, which cannot perform protective functions in the body. This review is devoted to the analysis of modern approaches aimed both at increasing the level of HDLs in blood plasma and at maintaining and restoring their native functional properties.

Keywords: high density lipoproteins, approaches to increase antiatherogenic function.

Introduction. Large epidemiologic studies have demonstrated an inverse relationship between the concentration of serum cholesterol (Chol) in high density lipoproteins (HDLs) and the risk of developing cardiovascular diseases (CVDs). Each increase in the concentration of HDL-Chol by 0.026 mmol/l decreases the risk of developing coronary heart disease (CHD) by 2–3% [56]. In this connection, various approaches were devised to increase the HDL-Chol level. However, recent studies, particularly those where the transfer of Chol esters (eChol) was estimated using an inhibitor of cholesteryl ester transfer protein (CETP), revealed that an increase only in the level of HDL and HDL-Chol does not prevent cardiovascular diseases [48]. At present, the research interest is focused on estimating the functional state of HDL and HDL-Chol rather than their level.

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The main antiatherogenic function of HDLs is related to the reverse Chol transport (RCT); in addition, they possess antioxidant, anti-inflammatory, antithrombotic and anti-infectious functions, which also determine their atheroprotective action [6,8]. HDLs enhance the production of nitric oxide (NO), stimulate proliferation and migration of endothelial cells, and suppress inflammation and apoptosis processes [39]. HDL-associated enzymes paraoxonase 1 (PON-1), lecithincholesterolacyltransferase (LCAT), platelet-activating factor acetylhydrolase (PAF-AH), and myeloperoxidase (MPO) are responsible for the antioxidant functions [45]. Antidiabetic [22,38] and cardioprotective functions of HDLs are discussed [6].

The aim of this review is to analyze therapeutic approaches to restoring the native structural-functional properties of HDLs. Among such approaches are physical exercise and low-calorie diet, CETP inhibitors, and raising the level of apolipoprotein A-I (apoA-I) with the use of recombinant HDLs (rHDLs) or apoA-I mimetic peptides.

Physical exercise. Regular physical exercises and diet not only increase the level of HDL-Chol but also improve the functional properties of lipoprotein particles, particularly HDLs [29]. Different researchers have demonstrated that the HDL level significantly increases after a training load. Sportsmen showed a higher maximum oxygen consumption (VO_2max), concentrations of HDL-Chol and apoA-I in blood plasma were also higher; along with this, the efficacy of RCT increased due to a growth in the amount of large mature α1-HDL particles that deliver Chol esters to the liver [29,20]. In women with obesity, physical exercise for 9 weeks (5 sessions a week) reduced their body weight and decreased the concentration of triglycerides (TG) and apoB; therewith, the content of total Chol, LDL-Chol and HDL-Chol did not change. However, RCT has improved; this was estimated from the HDL ability to remove $^{(14)}$C-Chol from the human monocyte/macrophage line THP-1 [42]. In marathoners, the concentrations of LDL-Chol, apoB and TG did not differ from the control group of patients with a sedentary lifestyle. However, marathoners had higher levels of HDL-Chol and apoA-I; therewith, an increase in the transfer rate of labeled lipids (Chol, eChol, TG, and phos-

pholipids (PLP)) from donor blood serum to HDLs of sportsmen was observed [53].

HDLs were shown to protect the vessel endothelium in patients with chronic cardiac insufficiency (CCI) in response to physical exercise. At the beginning of the study (before physical exercises), the patients showed a substantial decrease in the NO production by human aortic endothelial cells (HAEC) upon incubation in the presence of HDLs isolated from CCI patients. HDLs taken from patients slightly stimulated the phosphorylation of Ser(1177), Thr(495), PKC-ßII-Ser(660) and p70S6K-Ser(411) in endothelial NO synthase (eNOS). The production of nitric oxide (NO) virtually reduced to zero. Daily training during 15 weeks considerably improved the ability of HDLs to activate eNOS and increased the production of NO in HAEC [2]. In comparison with the control group, blood plasma of patients with metabolic syndrome (MS) showed a high level of TG, a low concentration of HDL-Chol, and a low activity of paraoxonase-1 (PON-1) in HDLs. After three months of moderate intensity training without any specific diet, a decrease in the TG level without changes in HDL-Chol and LDL-Chol was observed. However, physical exercises increased the transfer of free Chol to HDLs and enhanced the activity of PON-1 in them [12].

A positive correlation was found between aerobic exercises and enzymes involved in the regulation of RCT (LCAT, CETP, and lipoprotein lipase (LPL)) [29]. An important role in RCT is played by ABCA1 and ABCG1 transporters and SR-B1 receptors. Experimental models performed with Wistar rats revealed an increase in the concentration of HDL-Chol, apoA-I, pre-β-HDL particles and LCAT in blood serum after six weeks of aerobic training with physical exercise. An increased expression of mRNA of ABCA1 transporter was observed in the animals' liver and intestines. After 12 weeks of aerobic training, expression of the ABCA1 gene increased also in the heart [17]. An increased expression of SR-B1 and ABCA1 genes was observed in spayed rats after eight weeks of aerobic training [33]. Physically active persons have higher concentrations of apoA-1 and ABCA1 mRNA in leucocytes as compared to people with a sedentary lifestyle. Moreover, a positive correlation was found between ABCA1 in leucocytes with pre-β-HDL and activity of LCAT, as well as between apoA-I and RCT [21]. In mice with the type 2 diabetes model, physical training also increased expression of the ABCA1 gene [55].

It was shown that physical exercise increases the gene expression and the content of PPAR-alpha (Peroxisome Proliferator – Activated Receptor α) in the liver, which plays an essential role in the metabolism of HDL [55]. The PPAR nuclear transcription factors enhance the synthesis of main HDL proteins, thus facilitating RCT. In addition, PPAR-α boost the HDL capture by the liver [7]. PPAR-α are also involved in the regulation of inflammation processes, expression of cell adhesion molecules, and production of chemotaxis factors; in addition, they suppress the proliferation of smooth muscle cells and the activity of fibroblasts. Their activation may promote the regression of atherosclerotic plaques [7]. In people with a sedentary lifestyle, the prolonged low intensity aerobic exercises activate PPARγ and lead to a positive modulation of receptors CD36, transporters ABCA1 and ABCG1, which are directly involved in RCT [10].

Thus, physical exercises accelerate RCT, which is related to an increase in the concentration of apoA-I, activity of enzymes (LCAT, LPL), and expression of ATP-binding cassette transporters ABCA1 and ABCG1. Strengthening of physical activity improves the ability of HDL to activate eNOS and NO production, thus affecting the state of endothelium-dependent vasodilation. In addition, the indicated conditions increase the activity of PON-1 and the antioxidant activity of HDL subfractions.

Low-calorie diet. Nutrition plays a key role in the metabolism of lipoproteins, particularly HDL. Each kilogram of the body weight loss increases HDL-Chol by 0.01 mmol/l (0.4 mg/dl). Aerobic physical exercises, such as 25-30 km of sharp walk per week (or an equivalent activity), also promote weight reduction and increase the level of HDL-Chol by 0.08-0.15 mmol/l (3.1-6 mg/dl) [1]. In obese women, intense physical exercises decreased the body weight from 2.3 to 15.5 kg, on the average. A significant correlation was found between body weight losses and RCT [42].

A one-year randomized controlled study PREDIMED monitored the functions of HDLs after conventional antioxidant-rich Mediterranean diet. The study revealed an increase in RCT relative to the initial level, a decrease in activity of CETP, an increase in activity of LCAT and PON-1, and the ability of HDL to induce a release of NO in endothelial cells. Thus, the Mediterranean diet was shown to improve atheroprotective functions of HDLs [20]. In men with excess body weight and obesity, 12 weeks of a low-calorie diet decreased not only the body weight, but also the level of microRNA (miR-223) in HDLs. MiR-223 is represented by small endogenous noncoding RNA that are associated with metabolic disorders in the case of obesity [46].

A pronounced decrease in the body weight after bariatric surgery also restores the HDL functions. Bariatric surgery – the Roux-en-Y gastric bypass (RYGB) – is a surgical operation leading to a considerable decrease in the gastric volume and amount of absorbed nutrients. A retrospective observation of adult patients with obesity and type 2 diabetes showed a decrease in the frequency of macro- and microvascular complications of diabetes in the group of patients after RYGB [3]. It was demonstrated in experimental models that RYGB facilitates an early improvement of the HDL function, including their anti-apoptotic, antioxidant and anti-inflammatory activity as well as the ability to transfer cholesterol. In addition, RYGB rapidly restores endothelial dysfunction and enhances the ability of HDL to produce NO. The restoration of the HDL function was stable for a long time after bariatric surgery [36].

Thus, RYGB or a considerable decrease in the excess body weight achieved with the use of a low-calorie antioxidant-rich diet is aimed to increase the HDL level, enhance RCT and lower the activity of CETP. In the process, the activity of LCAT and PON-1 enzymes and the ability of HDLs to induce NO production by endothelial cells are also improved.

The effect of niacin (nicotinic acid – NA, vitamin B3). The main target organs for NA are liver and adipose tissue. In the liver, NA inhibits diacylglycerol acyltransferase 2, thus hindering the secretion of very low density lipoproteins (VLDL) and lowering the LDL level in blood plasma. Therewith, the level of HDL-Chol and apoA-I in blood plasma considerably increases by stimulating the synthesis of apolipoproteins in the liver [1].

An early assessment of the niacin monotherapy for reducing the CVD risk happened to be promising. In a randomized placebo-controlled study (Coronary Drug Project), the 15-year observation demonstrated the following advantages of NA monotherapy: it decreased the occurrence of CVD and reduced the risk of lethal outcomes [11]. According to the meta-analysis published in 2010, a long-term administration of NA decreased the frequency of cardiovascular complications by 25% [9]; in a combination with statins, it promoted the regression of atherosclerosis estimated from changes in the carotid artery intima-media thickness [6]. However, later studies did not confirm

the positive clinical effect of monotherapy with this preparation; moreover, the number of serious unwanted effects (hot flashes to the head, neck and upper part of the body) increased. Side effects of NA are attributed to the formation of a large amount of prostaglandin D2 (PGD2); as a result, the niacin therapy did not become popular [52]. The sustained release forms of niacin in a combination with laropiprant (a selective antagonist of the PGD2 receptor) have been developed to suppress the side effect. However, a study on the efficacy of the Tredaptiv (NA + laropiprant) preparation did not reveal additional advantages when the preparation was added to therapy with statins. Besides, in the group of patients cured with niacin and laropiprant, the development of insulin resistance was observed and the risk of diabetes increased by 32%. Therapy by the Tredaptiv preparation increased the risk of other side effects, including myopathy, gastrointestinal hemorrhage, stroke and infections [52].

Examination of healthy volunteers revealed that therapy with the (NA + laropiprant) preparation at a dose of 2 g/day during 16 weeks produced a typical effect on the lipid characteristics (HDL-Chol increased by 16%, LDL-Chol decreased by 20%, and TG decreased by 15%); however, apoA-I was replaced by SAA (Serum Amyloid A) in the composition of HDL [19]. The HDL particles enriched with SAA are dysfunctional, they lose atheroprotective properties of native HDLs and can act as proinflammatory agents [40]. A J774 macrophage culture and a primary culture of endothelial cells of bovine aorta were used to demonstrate that niacin does not affect the outflow of Chol from the cells. Niacin did not activate the phosphorylation of eNOS (Ser1179) and Akt (Ser473); therefore, it does not affect the ability of HDL to improve the function of endothelium. These facts may explain the absence of cardioprotective effect of the NA therapy [19].

By now, none of the medicinal preparations containing NA has been approved [52].

The role of CETP inhibitors. A glycoprotein that carries Chol esters (CETP) is synthesized in the liver and plays an important role in the transfer of eChol and TG between lipoproteins. Chol esters are transferred from HDL to potentially atherogenic VLDL and LDL particles, which are then removed with the use of LDL liver receptors (LDLR). The inhibition of CETP decreases the transfer rate of eChol from HDL to TG-rich lipoproteins, thus increasing the content of eChol in HDL. The inhibition of CETP or the CETP gene knockout in rabbits decreases the intensity of atherosclerosis of aorta and coronary arteries even at a diet with high Chol content [48]. A genetic polymorphism determining the low level or activity of CETP is accompanied by a higher concentration of HDL-Chol and a low concentration of LDL-Chol in blood, which reduces the risk of developing CHD. This formed a basis for the development of medicinal preparations belonging to the class of CETP inhibitors, the application of which was expected to reduce the risk of CVD complications [48,6,24].

Four CETP preparations have passed through phase III trials, but the results for two of them – dalcetrapib and torcetrapib – were negative. Although an increase in HDL-Chol and apoA-I (the main HDL protein) was observed, the ILLUMINATE study of CVD patients cured with torcetrapib was stopped prematurely. An electrolyte imbalance, an increased concentration of aldosterone in blood plasma, hypertension, and frequent heart attacks were observed in patients in comparison with the control group obtaining atorvastatin [5]. In the dal-OUCOMES study, therapy with the CETP inhibitor, dalcetrapib, did not reduce the risk of complications and mortality from CVD despite the absence of side effects in comparison with torcetrapib. This study was also stopped prematurely due to the evident ineffectiveness of the preparation [43].

The ACCELERATE study estimated the efficacy of a powerful CETP inhibitor – evacetrapib. Administered in a high dose (500 mg/day) as a monotherapy, it increased the HDL-Chol level and decreased LDL-Chol. However, the observation was also stopped approximately after two years because it was inefficient in reducing cardiovascular events [27].

The REVEAL study dealt with the action of anacetrapib. The use of anacetrapib increased the level of HDL-Chol more than twofold, and that of apoA-I by 36%. Efficacy and safety of the preparation were investigated during four years. No side effects of anacetrapib were observed in the study. Anacetrapib showed a moderate decrease in the main cardiovascular complications already in the first year of therapy and a considerable decrease during four years as compared to placebo [51]. The mechanism of the beneficial effect of anacetrapib is attributed to improvement of the qualitative composition of HDL. In persons cured with anacetrapib, HDLs increased RCT from the macrophages loaded with Chol by a factor of 1.5 – 2 [48]. Other inhibitors of CETP – evacetrapib and TA-8995 – increased the RCT rate by 34 and 50%, respectively [6]. It was noted that HDLs retain their anti-inflammatory and antioxidant properties during the administration of CETP inhibitors [6,51].

An important positive effect produced by CETP inhibitors is a decrease in the level of glycated hemoglobin, glucose and insulin resistance index (HOMA-IR). Thus, CETP inhibitors can prevent the prodiabetogenic effect of statins and niacin [30]. In this connection, investigation of the effect of various CETP inhibitors on the functional properties of HDLs is considered to be promising.

The effect of recombinant HDLs. The effect of the phospholipid apoA-I complexes with a low content of lipids, the so-called recombinant HDLs (rHDLs), was earlier studied using experimental models with animals. Intravenous infusion of rHDLs and an increase in the apoA-I level in transgenic animals were shown to enhance RCT from macrophages, which is accompanied by a pronounced regression of atherosclerosis in mice and rabbits [6,37,13].

Chen and co-authors [13] studied the effect of the CSL-111 preparation, which is a complex of native apoA-I with soybean lecithin. A single infusion of CSL-111 at a dose of 80 mg/kg decreased the volume and changed ultrasonic characteristics of a plaque [13]. Similar results were obtained in the case of four weekly infusions of CSL-111 at a dose of 40 mg/kg in patients with coronary atherosclerosis [44]. In patients after atherothrombotic stroke or acute myocardial infarction, four weekly infusions of 40 mg/kg CSL-111 increased the mobilization of endothelial progenitor cells, which led to restoration of endothelium and neovascularization [16]. In patients with atherosclerotic lesion of peripheral arteries of the lower extremities, even a single infusion of the preparation considerably decreased in 5–7 days the Chol content and expression of cell adhesion molecules (VCAM-1) in plaques [14]. Clinical trials of the improved CSL-111 species, the so-called CSL-112, are being performed now. Intravenous infusion of CSL-112 was shown to increase fourfold the ABCA1-mediated outflow of Chol [18].

rHDLs (CER-001), which are the modified negatively charged lipoprotein particles containing recombinant human apoA-I and natural phospholipids, have been proposed. In mice on a diet with high Chol content, CER-001 were shown to promote RCT [50]. In patients with familial hypo-alpha-lipoproteinemia, the CER-001 therapy not only increased the Chol content in HDL but also accel-

erated RCT. In addition, a considerable decrease in the activity of inflammation in aortic and carotid plaques as well as a decrease in the wall thickness of the carotid artery were found [26]. A similar effect was obtained for patients with homozygous familial hypercholesterolemia [23]. In patients with acute coronary syndrome (ACS), six weakly infusions of CER-001 at a dose of 3 mg/kg facilitated a decrease in the total volume of atheroma as compared to placebo [49,25,31].

Of particular interest are rHDLs containing apoA-I *Milano* (ETC-216), which differs from the wild-type apoA-I by arginine substituted for amino acid cysteine in position 173. The distinctive feature of this rHDL species is a longer removal from blood. The apoA-I *Milano* mutation was first detected in a cohort of Italians with low occurrence of atherosclerosis despite a very low level of HDL-Chol [47]. Intravenous infusion of ETC-216 substantially decreased the content of lipids in atheromatosis plaque and led to a rapid and pronounced regression of atherosclerosis in rabbits and mice [49]. Five weekly intravenous infusions of ETC-216 at a dose of 15 mg/kg to patients with ACS also produced a significant decrease in the volume and average maximum thickness of atheroma of the coronary vessels [35]. It should be noted that in some studies the infusion of rHDLs with apoA-I *Milano* did not exert a distinct positive effect. Thus, in the studies carried out in 22 hospitals of Canada and Europe, intravenous infusion of the standardized rHDL containing apoA-I *Milano* (MDCO-216) to the patients with ACS who received statins did not lead to a regression of atherosclerotic plaques [31].

A new rHDL species, which was called tetranectin-apoA-I (TN-apoA-I), is being tested now. This species was created by merging three apoA-I molecules with human protein tetranectin and phospholipids in different ratios. The TN-apoA-I complex is not filtered from blood by kidneys and has a longer half-life, which potentially increases its efficacy. It was shown that TN-apoA-I stimulates RCT, activates LCAT and exerts anti-inflammatory effect [37]. In rabbits, a single intravenous infusion of TN-apoA-I stabilized atherosclerotic lesions due to a considerable decrease in the migration of monocytes and the content of macrophages in carotid artery plaques. The quantitative estimation of RCT in rabbit plasma samples, which was carried out using the mouse macrophage line J774, revealed that TN-apoA-I significantly increases the Chol outflow via the ABCA1-mediated route. In addition, the infusion of rHDL considerably decreased the endothelial expression of cell adhesion molecules (VCAM-1, ICAM-1 and MCP-1), exerting the anti-inflammatory effect and protecting the endothelial cells [37]. rHDLs are supposed to induce an antioxidant protein 24-dehydrocholesterol reductase (DHCR24) in endothelial cells, thus enhancing their anti-inflammatory properties [41].

Therefore, studies demonstrate that rHDLs are the efficient Chol acceptors of macrophages, increase RCT and exert anti-inflammatory action on the artery wall.

The use of apoA-I mimetics. The apoA-I mimetic peptides are the artificially synthesized peptides possessing the biological properties of native apoA-I. The most studied and efficient preparation among mimetic peptides is D-4F, which comprises 18 amino acids, including four phenylalanine (F) residues. This peptide is not destroyed by digestive enzymes and can penetrate into plasma at oral administration [54, 15]. D-4F shows antiatherogenic effects similar to native HDLs: it accelerates the formation of pre-β-HDL, increases RCT, enhances the expression of eNOS and the production of NO, and suppresses the development of oxidative stress. The mechanism of D-4F antioxidant action is associated with the activation of heme oxygenase 1 (HO-1) enzyme, which neutralizes reactive oxygen species induced by the oxidized LDLs, which prevents the development of apoptosis in endothelial cells and promotes the restoration of their functions. It was shown that D-4F facilitates the migration and reparation of HAEC by inhibiting the expression of cell adhesion molecules and monocyte chemotactic protein 1 (MCP-1) [28].

RVX-208, which is also a small synthetic molecule, has been developed at the Resverlogix Corporation laboratory (Calgary, AB, Canada) for the treatment of ACS, atherosclerosis and Alzheimer's disease. A peroral preparation RVX-208 selectively activates the nuclear transcription factor, which increases the hepatic and intestinal production of apoA-I. In HepG2 cells, the RVX-208 preparation induced the synthesis of mRNA of apoA-I and protein, thus increasing the level of pre-β-HDL and α-HDL [34]. In African green monkeys receiving RVX-208 (at a dose of 7.5, 15 and 30 mg/kg twice a day or 60 mg/kg once a day during two months), the level of apoA-I and HDL in blood serum increased by 57 and 92%, respectively. Therewith, the incubation of macrophages in the presence of serum taken from these animals enhanced RCT [4]. The Ib/IIa phase clinical study demonstrated safety and good tolerance of RVX-208. In healthy volunteers, this preparation considerably increased the amount of apoA-I and pre-β-HDL and intensified the outflow of Chol from macrophages [34]. Unfortunately, patients with CHD, in contrast to monkeys, did not show a considerable increase in the apoA-I level even when a high dose of RVX-208 was administered. In addition, high doses of the preparation increased threefold the level of serum transaminases. A promising result of this study was the revealed increase in RCT (approximately by 20%), which was caused most likely by rapid maturation of HDLs [32].

Thus, an increase in the apoA-I level at intravenous infusion of rHDL or apoA-I mimetic peptides produces a beneficial effect on RCT, the function of endothelium and the regression of atherosclerotic plaque. The improvement of the function of endothelium under the action of apoA-I may proceed via the activation of intracellular signaling pathways associated with the regulation of inflammation and apoptosis.

Conclusion. Experimental and clinical studies have demonstrated that a significant role in pathogenesis of atherosclerosis and, hence, cardiovascular diseases is played by the modified or dysfunctional HDLs. Such HDLs lose their antiatherogenic, antioxidant and anti-inflammatory properties. Several approaches to restoring the lost functions of HDL are known. Some of them are simple but quite effective: intensification of physical activity and a diet promoting a decrease in excess body weight. In recent years, it was proposed to correct lipoprotein metabolism with the use of CETP inhibitors, apoA-I mimetic peptides, rHDLs and HDLs containing apoA-I *Milano*. Such therapeutic approaches make it possible not only to increase the level of HDLs and apoA-I in blood plasma, but also to enhance their antiatherogenic action by accelerating RCT, increasing the activity of LCAT and PON-1 enzymes, and restoring the functions of vascular endothelium. However, additional clinical trials are required to estimate safety and efficacy of these approaches.

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POINT OF VIEW

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«RIGHT NOT TO KNOW» AS AN ETHICAL PRINCIPLE FOR DNA TESTING OF LATE-ONSET DISEASES

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The article examines the ethical principle - the "right not to know", associated with DNA testing of diseases with late onset of development, based on the materials of foreign publications. For geneticists and doctors of the Republic of Sakha (Yakutia), this problem will require discussion and decision-making, since type I spinocerebellar ataxia - a hereditary late manifestation disease, DNA testing of which has been used in practical medicine of the republic since the 2000s - is widespread in the population. Huntington's chorea is the most researched hereditary disease on bioethical issues. According to experts, it is necessary to update the recommended testing guidelines for Huntington's chorea in the context of the principle of “right not to know” with a joint committee of geneticists, neurologists, and legal and ethical experts.

Keywords: bioethics, right not to know, DNA testing, prenatal diagnostics, Huntington's chorea, spinocerebellar ataxia type 1.

Introduction. The rapid development of molecular genetic research, high-throughput methods of genome sequencing and the widespread use of DNA diagnostics of various diseases is, undoubtedly, a mark of progress of science and practical medicine, but on the other hand, this further aggravates ethical problems of interference with the human genome, such as the autonomy of the individual, confidentiality of genetic information, moral and psychological consequences for the individual with a complex choice of decisions related to DNA testing [2,9, 36].

Throughout life, an individual can resort to various types of genetic testing, depending on the goals that he sets for himself: with the need to conduct DNA testing to find out the cause of his disease or detect a hidden genetic health issue, testing to establish kinship, testing to determine the compatibility of body tissues, to predict the tolerability of different drug options. Most often, people turn to medical genetic testing for diagnosing hereditary pathologies. Currently, with the help of DNA testing, a huge number of various diseases and predispositions are diagnosed [32,39]

In Russia, a small number of publications of a philosophical nature are devoted to the problem of the “right not to know”, in particular, there is an opinion that the predictive direction of medicine, based simultaneously on universal biological laws and personalized genetic preclinical diagnosis of potential pathologies of a particular person, will inevitably put the individual in a difficult moral and existential situation [6]. A rethinking of the currently established ethical and normative attitudes is taking place, taking into account the new possibilities of genomic medicine, and we are not talking about a return to paternalism, but asserting the need for a broader concept of autonomy, taking into account the existing restrictions on informing and understanding the family specifics of genetic information [1].

The purpose of this article is to discuss the ethical "right not to know" principle associated with DNA testing for late-onset diseases. For geneticists and physicians, this problem will definitely require discussion and decision-making, since In the Republic of Sakha (Yakutia), a hereditary disease with a late onset of development is widespread - type I spinocerebellar ataxia (SCA1), DNA testing of which has been used in practical medicine of the republic since 2000. Our research experience in the field of ethics of genetic counseling and DNA testing has revealed a complex layer of social, legal and psychological problems that require close attention of specialists [4,37].

The «Right not to know» Principle and DNA Testing of Hereditary Diseases. There are fundamental ethical principles associated with DNA testing of hereditary diseases: non-directiveness of genetic counseling, respect for individual autonomy, preservation of confidentiality of genetic information of any kind, the principle of fairness and awareness [2,

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