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POINT OF VIEW

S.K. Kononova

«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,

КОНОНОВА Сардана Кононовна – к.б.н., в.н.с.-зав.лаб. ЯНЦ КМП, konsard@rambler.ru

27]. For a long time, the doctor has been the patient's confidant, who entrusted him with his health. The professionalism of medical workers lies in their competence, the ability to protect the interests of not only their patients, but also the public interests, so as not to lose the trust of society in medicine as a whole [34].

In the last decade, with the onset of the "genomic era", there has been some transformation of established ethical rules. The most discussed and challenging for doctors and geneticists is the ethical principle of "the right not to know" [10,11]. Legal researcher Andorno (2004) writes: "The 'right not to know' statement may seem strange. Over the past decades, it has been strongly emphasized that the patient has the right to be informed about the risks and benefits of treatment or intervention and, on this basis, to give consent to them or not. Having reaffirmed the "patient's right to know" as a fundamental ethical and legal principle, we are now faced with a clearly opposite requirement. This happens, in particular, in the field of genetics: as the predictive power of genetic tests increases, more and more people learn that they are at risk of serious disease without any real chance to reduce this risk or receive effective treatment "[7,22].

Recent research in cognitive psychology has shown that people often prefer not knowing complete information. For example, a recent study showed that 85-90% would not want to know in advance what negative events will hit them in the future (eg, cause of death, divorce) [23]. However, the preference for not knowing about potentially threatening upcoming life events seems to be less pronounced in the context of genetic testing; genetic testing is generally positively assessed by the public [18]. It has been shown that the majority want to know about their results and that there is little difference between information about risk (e.g. information about the status of the carrier) and information about a possible diagnosis (e.g. about the onset of dementia) [15, 40]. Interestingly, some patients in the 50% risk group for Huntington's disease (HD) wanted to know their genetic status with any, even a positive result, according to them, they could plan further work and outline priorities in life [30,31,42]

The ethical principle of the "right not to know" is recognized in international and national legislation. According to the acts and conventions: - "everyone has the right to know any information received about his health, the wishes of individuals not to be informed about this must be respected"; "The patient has the right not to be informed at his / her direct request, unless it is required to protect the life of another person"; "The right of every person to decide whether or not to be aware of the results of genetic examination and the consequences arising from this should be respected" [30,31,41].

Nowadays, the entire human genome can be quickly sequenced and analyzed at a constantly decreasing financial cost. Such high-performance methods are very likely to lead to random findings and conclusions [21]. In a study by Hofmann, 2016, this is defined by the expression "incidental findings of uncertain significance" (IFUS) - random inferences of uncertain significance. As an example, consider a case published in The New York Times in 2014. *"Jennifer was 39 years old and she was perfectly healthy, but her grandmother died young from breast cancer, so she decided to get tested for mutations in two genes known to increase the risk of the disease. When a genetic consultant suggested additional tests for 20 other genes associated with various types of cancer, Jennifer said yes. "The more information the better", - she thought. The results, she said, were "surreal." She did not have mutations in her breast cancer genes, but one of the genes was associated with a high risk of stomach cancer. In people with a family history of the disease, this mutation is considered so risky that patients who are not even sick are often advised to have their stomachs removed. But no one knows what this discovery might mean in someone like Jennifer, whose family did not have this disease "[24].* As you can see, genomic technologies are producing unexpected finds, such as cancer susceptibility genes, that have clinical implications for those tested and their families. Whether people or their families who were seeking for a test are ready to know these results remains questionable [16, 22, 26]. In a Canadian sample of patients from burdened families with HD, a three-year program of predictive and prenatal DNA testing for HD was conducted - 88% of patients from this sample refused the predictive DNA test [17]. In another study, when questioning participants in a hypothetical scenario on the problem of presymptomatic diagnosis of incurable diseases, 50% of respondents would not want to receive negative information about their health, including the diagnosis of HD. The reasons were as expected - incurability of the disease, fear of disability, possible depression and stress [43]. Melnyk (2012) showed that: lack of resources for coping with the disease, expected regret and learning about uncontrolled predictors were associated with avoidance of information about the risk of breast cancer [16,33]. In other reports, the specific decision on the need to find out genomic information by an individual in hypothetical scenarios representing cases of disabling diseases with late onset was clearly predetermined by the characteristics of the disease scenario, namely "ability to control the disease" and "DNA test accuracy" [12,22].

Failure to disclose positive results can be problematic for both genetics physicians and those conducting genetic testing. It is a difficult ethical situation when they work within medical ethical boundaries based on the principles of autonomy, charity and fairness [27, 38].

The ethical principle of the "right not to know" is also linked to the problem of DNA testing of minors. In studies of bioethical problems of medical and genetic counseling of patients at risk of SCA1, several precedents of presymptomatic DNA testing of minors in families with SCA1 have been described. One of them was associated with the mother's understandable desire to protect her daughter from psychological stress during her future admission to a higher educational institution. The mother believed that if her daughter is a carrier of the SCA1 mutation and becomes ill in adulthood, then it makes no sense for her to make efforts to get higher education. With this attitude, the girl's mother asked to reveal the results of DNA testing to her, but the request was refused, because this precedent was regarded as involuntary discrimination within the girl's own family. The next case was connected with the transfer of a boy from boxing to a less traumatic sport at the convincing request of his parents, who were very worried about the result of the DNA test and the health of their son. Despite the principle of non-disclosure, doctors had to satisfy the parents' request to disclose the child's genetic status. The cases described reveal complex ethical problems, the solution of which depends on the level of education of the parents, on the material support of the family and on many different nuances that doctors may not know about. It is not excluded that a family has a special attitude towards a child, the possibility of discrimination in obtaining education or in the field of insurance. Premature disclosure of his genetic status to a child can lead to a loss of confidence, self-identification in society, distortion of values and goals in life [8, 20, 29].

«Right not to know» in prenatal diagnosis of diseases with late onset of development. Since 2002, in clinical

medicine of the Republic of Sakha (Yakutia), prenatal diagnosis (PD) of type I spinocerebellar ataxia has been carried out in compliance with the fundamental bioethical principles: full informing the family about the PD procedure, the priority right of the pregnant woman to decide on the fate of the fetus, performing the PD procedure in the early stages up to 12 weeks pregnancy, patient autonomy and confidentiality [29]. However, we do not exclude the emergence of more complex ethical situations in PD SCA1 associated with presymptomatic DNA testing of carriers of the mutation in the *SCA1* gene.

For a more complete disclosure of the issue, let us turn to the research of ethical problems of PD of another neurodegenerative disease - Huntington's disease (HD), which also belongs to the group of monogenic diseases with dynamic mutations and late onset of development, like SCA1. The case described by Erez et al., (2010) raises an important ethical question: is there a right to genetic ignorance (the right not to know) when it puts others (partner) at risk of unnecessary medical procedures.

A 34-year-old woman went to an antenatal clinic for genetic counseling. She was 12 weeks pregnant and recently found out that her husband's father had HD. After receiving genetic counseling, she and her husband underwent prenatal fetal testing. The results of the examination of the husband showed that he had no risk of developing HD and, as expected, the fetus also had no risk of developing HD. This is a case of familial HD, when a proband at risk chose not to know his disease status, but wanted to know the status of his unborn child. Three years later, the couple returned to antenatal consultation to receive pre-implantation genetic diagnostics (including in vitro fertilization) for future pregnancies, while the proband's spouse had to undergo an unnecessary procedure and, accordingly, an unjustified risk to her health.

In this case, doctors are faced with a dilemma of how to use the accumulated experience in favor of the patient, without subjecting him to unnecessary procedures and at the same time try to disclose information useful for the family in the most delicate way in order to make it possible to make the most correct decision on the procedure for prenatal testing and further prospects[21,35].

HD is not only the most studied hereditary disease on bioethical issues, but also the most advanced in terms of interaction of researchers and doctors with the Association of HD burdened families and patients with [35].

Historically, back in 1985 in France and in 1989 in Canada, an international group for the study of Huntington's Disease at the World Federation of Neurology discussed bioethical and legal issues related to scientific research in HD. As a result, a set of ethical principles and rules for presymptomatic DNA testing of HD was adopted. These rules were recommended to be followed not only by doctors - geneticists and specialists performing DNA testing, but also by patients at risk for HD, since the interests of both the doctor and the person being tested were respected. Later, significant progress was made in the development and implementation of direct DNA diagnostics in medical practice, this analysis has become a routine procedure. In 1994, an expanded and refined protocol of DNA testing and medical genetic counseling for HD became the main document for specialists in many countries, where it was possible to organize molecular genetic laboratories [14, 25, 28].

Now, in the era of genomics and the application of high-throughput genome sequencing, experts believe it is time to return to the issue of updating the recommended guidelines for HD testing by a joint committee of geneticists, neurologists, and legal and ethical experts. It is proposed to focus the attention of specialists on the following points: the key specialists in the consultation process should be: a geneticist, psychologist, and neurologist. In order to reduce the risk of unnecessary testing on the parent and fetus, it is imperative to confirm the diagnosis of HD in the family. Most genetic tests are most informative if a clinically affected family member is tested first before using the test to predict genetic status for a clinically unaffected family member. When considering prenatal testing, the procedure and cell type affect the interpretation of the results. In HD, there is a category of intermediate alleles that can potentially spread to a range of diseases within a single generation. Genetic counseling of the highest standards should be available in every country and provided by a specialized genetic counseling unit. Joint discussion of the issue between the consultant and the consulted should be aimed at obtaining free and informed consent of the test taker to conduct DNA testing. Obtaining a positive DNA test result should not be an obstacle to childbearing if the tested person has made a decision to prolong the pregnancy [35].

Conclusion. The “right not to know” is widely discussed in foreign literature, there are both supporters and opponents of this ethical principle. The arguments “for” the compliance with the principle are, first of all, the fears of violating basic ethical principles, namely, the rights and autonomy of the individual. There will be an inevitable increase in paternalism in medical practice, as well as the loss of the principle of confidentiality of genetic information. It will be impossible to assess the moral and psychological suffering of the patient, especially when he undergoes pre-symptomatic DNA testing of an incurable disease. On the other hand, experts in this field - opponents of the principle of "the right not to know", believe that the patient should be fully informed about any disease, hiding data that is important to relatives also violates their rights and risks unnecessary procedures, such as prenatal or pre-implantation diagnostics.

Talks and discussions will continue, the ethical rules of DNA testing, whole genome DNA sequencing and related "random findings" of the human genome will be researched. Bioethical research is especially relevant in the Republic of Sakha (Yakutia), where routine DNA testing and prenatal DNA diagnostics of late-onset hereditary diseases are performed.

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