

# Regulatory and Legal Regulation of Assistance and Social Aspects of Medical Maintenance of Patients with Inborn Errors of Immunity: Case Study

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## ABSTRACT

Inborn errors of immunity (IEI) (primary immunodeficiency disorders [PIDs]) represent a group of more than 450 different diseases caused by defects in some components of the immune system. Together, they represent an important group of diseases that, if untreated, take a chronic nature, last for all life, and are characterized by a severe course with fatal consequences. In the case of untimely or incorrect diagnosis of these diseases, the life and health of patients depend on the quality and timeliness of the assistance provided. On the other hand, the absence of well-functioning mechanisms for accompanying such patients places a heavy burden on the healthcare system resources.

In this regard, the authors made an attempt to analyze the legal regulation and social conditions of medical support for patients with

IEI, including the article reflects the results of a survey of patients with IEI living in the Sverdlovsk region. Analysis of the results shows that this group of patients is experiencing serious difficulties with the disease diagnosis, prescribing disability, including obtaining adequate medical support because of the imperfection of Russian legislation.

**Keywords:** Inborn errors of immunity, Primary immunodeficiency disorder, Orphan disease, Legal regulation, Medical care

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## INTRODUCTION

Immunity is a complex of reactions, aiming at maintaining the constancy of the internal environment of the human body. Genetically determined defects in the immune system lead to primary immunodeficiency disorder (PID). PIDs are genetically determined diseases, which are based on genetic defects. Clinically, PIDs are characterized by the development of infectious processes, autoimmune diseases, and predisposition to the development of malignant neoplasms. Since the analysis of epidemiological and experimental data raises the fundamental question of the real pathogenesis of infectious diseases, some authors indicated that infectious diseases arise as a result of various congenital errors in immunity [1]. PID is often disguised as other diseases; thus, the practitioner often does not have the technical and informational ability to think of this pathology as a possible root cause of the disease [2].

Today, instead of the phrase “primary immunodeficiency disorder (PID),” the phrase “Inborn errors of immunity (IEI)” is more often used. These concepts can be used interchangeably. The most severe forms of PID-IEI can occur in children up to a year old, but this diagnosis is also made for adults. One of the most dangerous forms of PID is severe combined immunodeficiency (SCID). It usually leads to the development of infectious diseases and death of children in the first two years of life. However, there are examples of successful neonatal screening for SCID in children in the neonatal period, as in the United States, this diagnosis has been performed in 26 states since 2010 (T-cell recombination excision circles [TREC] test) [3]. Newborns have been screened for the diagnosis of congenital metabolic disorders in the United States for many decades, and SCID has already been included in the expanded Newborn Screening Program (NBS), but there are still some barriers to this test at the national level [4].

In the Russian Federation, neonatal screening of newborns for congenital genetically determined diseases is also carried out; however, such as many other types of PID-IEI, SCID is

not included in the extremely limited list of screened diseases. Naturally, the lack of well-functioning diagnostic mechanisms entails the lack of well-functioning mechanisms of treatment and medical support for patients with PID-IEI, which, in turn, entails their regular and humanly understandable dissatisfaction with their situation.

## MATERIAL AND METHODS

To study the real problems of patients with PID-IEI in the Russian Federation, as well as to clarify the causes of inter-institutional conflicts arising from the implementation of legal and ethical standards in the interaction of society and patients, the authors, by using special legal and comparative legal methods of scientific knowledge, analyzed the current Russian legislation governing the provision of care and medical support for patients with IEI (PID). Therefore, an analysis of the current Russian legislation governing the provision of care and medical accompaniment to patients with IEI (PID), as well as an applied sociological study, was conducted, in which residents of the Sverdlovsk region were interviewed, whose children suffer from IEI (PID) during neonatal screening by using the TREC/kappa-deleting element recombination circle (KREC) method.

The selection of parents was carried out according to the results of medical examinations obtained in the Sverdlovsk region over the past five years. In this regard, a questionnaire consisting of 61 questions, including five tabular questions and a large number of open questions (the answer is formulated by the respondent himself), was used in this study. The study was conducted in the II and III quarters of 2019 on the basis of medical organizations, which provide services to patients with IEI. The survey was subjected to adult visitors, including parents, relatives, legal representatives of children with IEI, and adult patients with IEI ( $n = 52$ ). The survey was conducted with a questionnaire.

## RESULTS AND DISCUSSION

Legal regulation of assistance and social aspects of medical support

The definition of orphan diseases and medicines (the prevalence of no more than five injured people per 10,000) was fixed in the European Union (EU) back in 1999 (Regulation EC No. 141/2000 of the European Parliament and the Council of the EU of December 16, 1999). Consequently, based on this regulation, people with orphan diseases could access to medicines. On the other, this regulation stimulates the pharmaceutical industry to research and produce orphan drugs. However, the mentioned regulation was not the first of its kind; some countries began this work earlier; for example, Japan initiated it in 1993 and the USA in 1983 [5]. In 1983, the National Organization of Rare Diseases (NORD) was established in the USA [6].

Nevertheless, nowadays, the legal instruments of the EU quite consistently uphold the interests of patients with orphan diseases and put them in a privileged position [7]. The European Working Group on Rare Disease Costing and Financing Processes (ORPH-VAL) has developed principles that encompass the decision-making criteria, decision-making process, sustainable financing system for the treatment of orphan diseases, and European coordination for this activity, which allows providing drugs to patients with rare diseases so that they could access to safe and effective methods of treatment like other people, suffering from other more common diseases [8].

To date, in article 44 of the Federal Law of November 21, 2011, No. 323-FL (as amended on May 29, 2019) “On the Basics of Protecting Citizens’ Health in the Russian Federation,” the concept is fixed as “rare (orphan) diseases,” which include diseases having a prevalence of no more than 10 cases of the disease per 100,000 population, as well as the concept of “life-threatening and chronic progressing rare (orphan) diseases, leading to a reduction in the life expectancy of citizens or their disability.”

The list of rare (orphan) diseases is compiled by the authorized federal executive body (Ministry of Health of the Russian Federation) on the basis of statistical data and is posted on its official website. Today, this list includes 216 diseases—the vast majority of which are genetically determined and actually incurable with the modern level of medicine.

The list of life-threatening and chronic progressing rare (orphan) diseases, leading to a reduction in the life expectancy of citizens or their disability (the so-called “List 24” or “regional list”), is approved by Decree of the Government of the Russian Federation of 04.26.2012 No. 403 (as amended on 20.11.2018), “On the procedure for maintaining the Federal Register of Persons Suffering Life-Threatening and Chronic Progressing Rare (Orphan) Diseases,” resulting in a reduction in the life expectancy of citizens or their disability. Its regional segment includes only 20 diseases today, while originally provided for 24 diseases. This list of 20 diseases, in accordance with the provisions of part 3 of article 44 and paragraph 10 of part 1 of article 16 of the Federal Law, “On the Basics of Protecting

the Health of Citizens in the Russian Federation,” implies an obligation, government bodies of constituent entities of the Russian Federation to organize, at the expense of their own budgets, the provision of citizens with medicines and specialized medical nutrition products for the treatment of these 20 life-threatening and chronic progressing rare (orphan) diseases, causing a reduction in the life expectancy of the citizen or disability.

In addition, in accordance with the provisions of part 7 of article 44 of the Federal Law, “On the Basics of Protecting the Health of Citizens in the Russian Federation,” a list of diseases (the so-called “List 7” or “federal list”) is separately allocated, including today such diseases as hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, malignant neoplasms of lymphoid, hematopoietic, and related tissues, multiple sclerosis, hemolytic-uremic syndrome, juvenile arthritis with systemic onset, and mucopolysaccharidosis of types I, II, and VI.

This list, by virtue of the provisions of part 10 of article 44 and paragraph 21 of part 2 of article 14 of the Federal Law, “On the Basics of Protecting the Health of Citizens in the Russian Federation,” is provided for the provision of citizens with medicines at the expense of the federal budget. Moreover, it should be noted that the above list of diseases (“federal list”) was expanded in 2018 by transferring to it part of the diseases from the list of life-threatening and chronic progressing rare (orphan) diseases, leading to a reduction in the life expectancy of a citizen or disability (“regional list”).

Thus, nowadays, in the Russian Federation, only 27 rare (orphan) diseases out of 216 recognized as such can expect full state support in treatment, and all of them are genetically determined. Accordingly, patients with the remaining 189 rare (orphan) diseases during their treatment cannot rely on effective assistance from the state if they are not recognized as disabled.

In line with this research, some authors also reported similar problems; for example, in the USA, there is also little interest in the study and production of orphan drugs. However, the creation of a number of regulatory acts, which stimulate and support drug manufacturers, has allowed stimulating research and development of new drugs for treatment [9]. Thus, in the United States in recent years, nearly 2000 products have been designated as drugs for the treatment of orphan diseases, and about 340 of them have received permission to sell [10].

SCID and other PID-IEI in the Russian Federation as independent diseases are not even included in the list of 216 rare (orphan) diseases, although, according to experts, they have the necessary signs for this [11]. Accordingly, PID-IEI patients can count on at least some state supports only if their disability is recognized in the prescribed manner.

The results of a sociological study

To understand the real problems of providing citizens with medicines, we have identified the degree of equipping PID-IEI patients with the necessary medicines and drugs. As follows from the data in Figure 1, the degree of equipping with them is not enough. Thus, less than a third of the families (28.1%) with PID-IEI patients are fully provided,

while 3.1% think that their family is not enough provided, and another 31.3% indicated that their family was provided with only some drugs. Thus, obtaining the necessary drugs for the prevention and treatment of a patient with PID-IEI for the vast majority of families is the main problem. It should be noted that the residents of Yekaterinburg are somewhat better provided with the necessary drugs than the

residents of the region. If informants of Yekaterinburg noted that they are fully provided in 38.9% of cases, then residents of the region only in 10%. The availability of drugs is also affected by the income—the higher the income, the better (according to informants) they are provided with the necessary medicines and drugs.

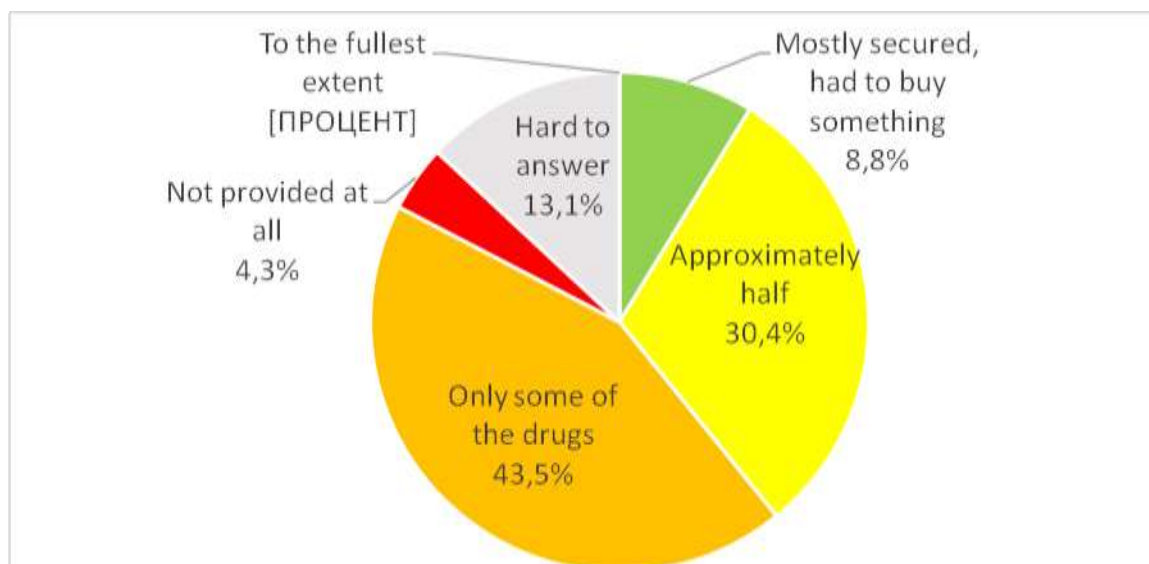


Figure 1: The degree of provision of IEI patients with the necessary medicines and drugs (the percentage of the number of respondents)

Another dependency that we were able to identify is much more problematic. As the data in Figure 2 show, the better the patient's health level, the higher the availability of medicines. This can be interpreted in another way: The lower the availability of medicines, the worse the health of a patient with PID-IEI is assessed. In other words, for some family members with PID-IEI, poor health is precisely the lack of the necessary drugs; for others, the situation probably develops as follows: The worse the health, the

more drugs are needed, and since there is no way to buy or get them, there is a problem of lack of drugs, which ultimately negatively affects the health of patients. We attempted to identify the groups of drugs that patients with PID-IEI need. In our opinion, we are mostly talking about drugs that stop the various effects of PID-IEI, and not about the drugs that treat or inhibit these diseases, so patients most of all need antihistamines (15.6%), antibiotics (12.5%), and enzymes (12.5%).

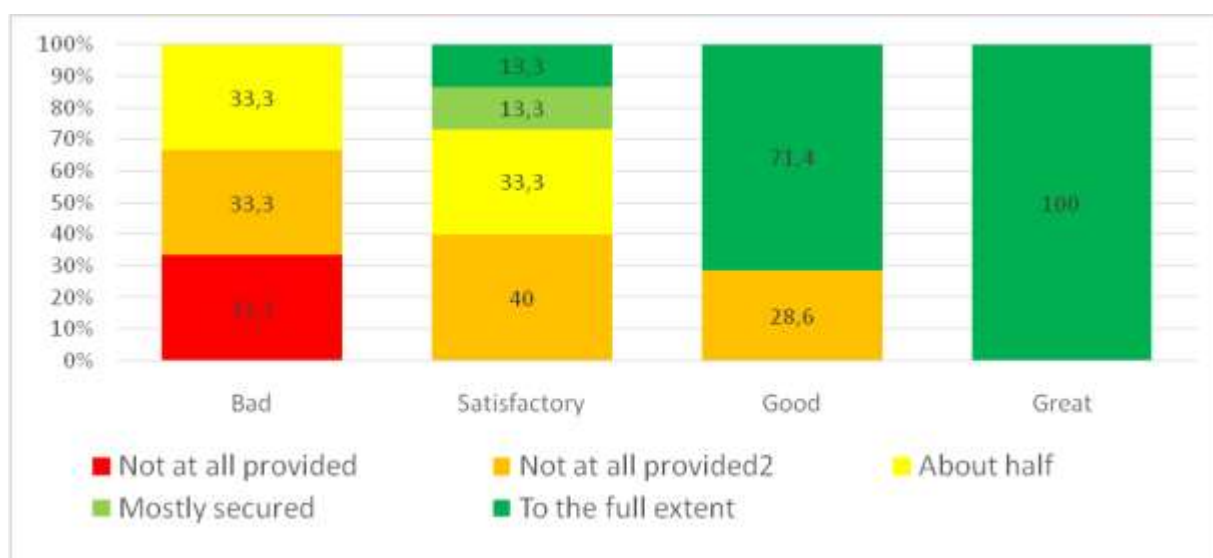


Figure 2: Provision of the necessary medications and drugs, depending on the assessment of the health level of patients with PID-IEI (the percentage of each level of health)

Thus, the lack of medical supplies is especially acute for residents of the region and low-income families and patients, whose health status, even within the study group, is below average.

However, in this regard, it should be noted that even the inclusion of the disease in one of the two above lists (“regional” or “federal”) in practice does not guarantee that the person suffering from it will receive the necessary treatment, and often for the basic life support, because of the actual incurability of the disease and expensive drugs at the expense of budget funds. There are several reasons for this as follows:

Firstly, the inaccuracy of the wording in the medical documentation and list of diseases. Thus, there are frequent cases when the form of a particular orphan disease is indicated in the patient’s medical documentation, which does not literally coincide with the wording from the list of such diseases, which leads to the loss of the possibility of budget support in the acquisition of expensive drugs.

Secondly, inadequate budgetary provision of expenditures of the budgets of the constituent entities of the Russian Federation for the purchase of medicines for people suffering from life-threatening and chronic progressing rare (orphan) diseases, leading to a reduction in the life expectancy of citizens or their disability (“regional list”).

This kind of problem arose exclusively in some regions of the Russian Federation and was resolved in court in favor of the plaintiffs. However, the cynicism of the situation was that, because of the length of court proceedings, many plaintiffs simply did not live to reach a decision without that necessary expensive drugs.

Thirdly, the availability of the necessary drugs and their quality. In addition to the bureaucratic and economic component in the lack of drugs for patients with PID-IEI, as our study shows, a number of factors also play a role, i.e., “doctors do not want to prescribe the necessary drugs,” according to 31.1% of informants from those families who do not have enough drugs, “doctors do not understand which drugs we need” (21.1%), and “there is a long line for the necessary drugs” (21.1%).

The problem of the availability and quality of the necessary drugs is by far the most acute and difficult to solve. Its essence lies in the fact that patients with diseases from the “federal” and “regional” lists often cannot be cured with the current level of development of medicine and need the constant (lifelong) provision of medicines that support their vital activity. The vast majority of such drugs were developed abroad and until recently had no domestic analogues, and many still do not have or will not have them because of the low profitability of their production.

Accordingly, the problem arises from the purchase, import, and legalization of state-owned drugs of foreign drugs on the territory of the Russian Federation, which, in turn, may be complicated by fluctuations in the ruble exchange rate, leading to a sharp substantial increase in the cost of the drug, or the establishment of prohibitions on its import for political considerations that have recently also become normal.

The problem of the quality of the domestic analogue drugs (the so-called generics), which are designed to solve the

problem of the purchase, import, and legalization of expensive foreign drugs, also remains an acute problem. Many patients complain of a large number of unexpected side effects up to the complete intolerance of the drug, especially with constant (lifelong) use or even their complete inefficiency compared to the original drugs [12].

In point 6.1 of part 1 of article 4 of Federal Law dated 12.04.2010 No. 61-Φ3 (as amended on 02.08.2019), “On the Circulation of Medicines” establishes the concept of “orphan drug,” that is, a medicine intended solely for the diagnosis or pathogenetic treatment of rare (orphan) diseases. In addition, in clause 6, part 1, article 4 of the Federal Law, “On the Circulation of Medicines,” the concept of “vital and essential medicines” is used, that is, drugs that provide priority health needs for the prevention and treatment of diseases, including those prevailing in the structure incidence in the Russian Federation. The list of such drugs is approved by the Government of the Russian Federation, which guarantees the purchase of such drugs at the expense of budget funds and state regulation of selling prices for them. Naturally, orphan drugs are rarely included in this list. In addition, the mentioned list changes extremely often, which creates practical difficulties for both patients and doctors, as well as for public authorities. It is indicative of the acute problem of prescribing patients, including patients with IEI-PID and orphan extremely expensive drugs for health reasons, that is, drugs that are not provided for by the standard of care for this specific disease.

In this case, the practice of the Supreme Court of the Russian Federation, which examined the dispute between the subject of the Russian Federation and the parent of a seriously ill child with a disability, is indicative.

Based on the circumstances of the case, the child was found having a rare (orphan) disease, which is not included in either the “federal” or “regional” lists, because of which he was recognized as disabled. Two consultations of doctors and the medical commission decided that the only possible treatment option is the use of a drug that is not registered in the Russian Federation and has no domestic analogues for life reasons. The Ministry of Health of the constituent entity of the Russian Federation refused to provide the specified drug at the expense of the constituent entity of the Russian Federation since the disease is not included in the list of life-threatening and chronic progressing rare (orphan) diseases, leading to a reduction in life expectancy or disability (“regional list”). The father of the child went to court. The first instance supported him, and the second did not. The Supreme Court of the Russian Federation did not agree with the court of the second instance, considered that the refusal of the Ministry of Health of the constituent entity of the Russian Federation violates the child’s right to life and protection of his health.

From the analysis of the practice of the Supreme Court of the Russian Federation, we can conclude that patients with IEI-PID can also apply for drugs at the expense of budgetary funds, including those prescribed for their vital indications, but only if they are recognized as disabled. However, this does not mean that patients with both IEI-PID and other rare (orphan) diseases will no longer have to go to court under similar circumstances. The position of the Supreme

Court of the Russian Federation considered above will only increase their chances of success.

In this regard, it should be noted that the application of judicial and pre-trial procedures requires not only time, strength, and desire of patients or parents of minor patients but also the necessary level of legal literacy, willingness, and ability to use knowledge of the law to protect their rights.

As the study showed, only 12.5% of informants evaluate the knowledge of their rights and duties of doctors in the framework of neonatal screening for hereditary diseases and only 10% in the framework of prenatal screening as “good

enough,” and none of the respondents rated them as “very good.” On the contrary, over 30% in the case of neonatal and 43% in the case of prenatal screening assess the knowledge of their rights and obligations of doctors as “I do not know at all.” Thus, we can conclude that most informants have insufficient knowledge about their rights and responsibilities of doctors in both neonatal and prenatal screenings. Expectedly better than others, informants with higher or incomplete higher education know their rights and obligations of doctors in screening.

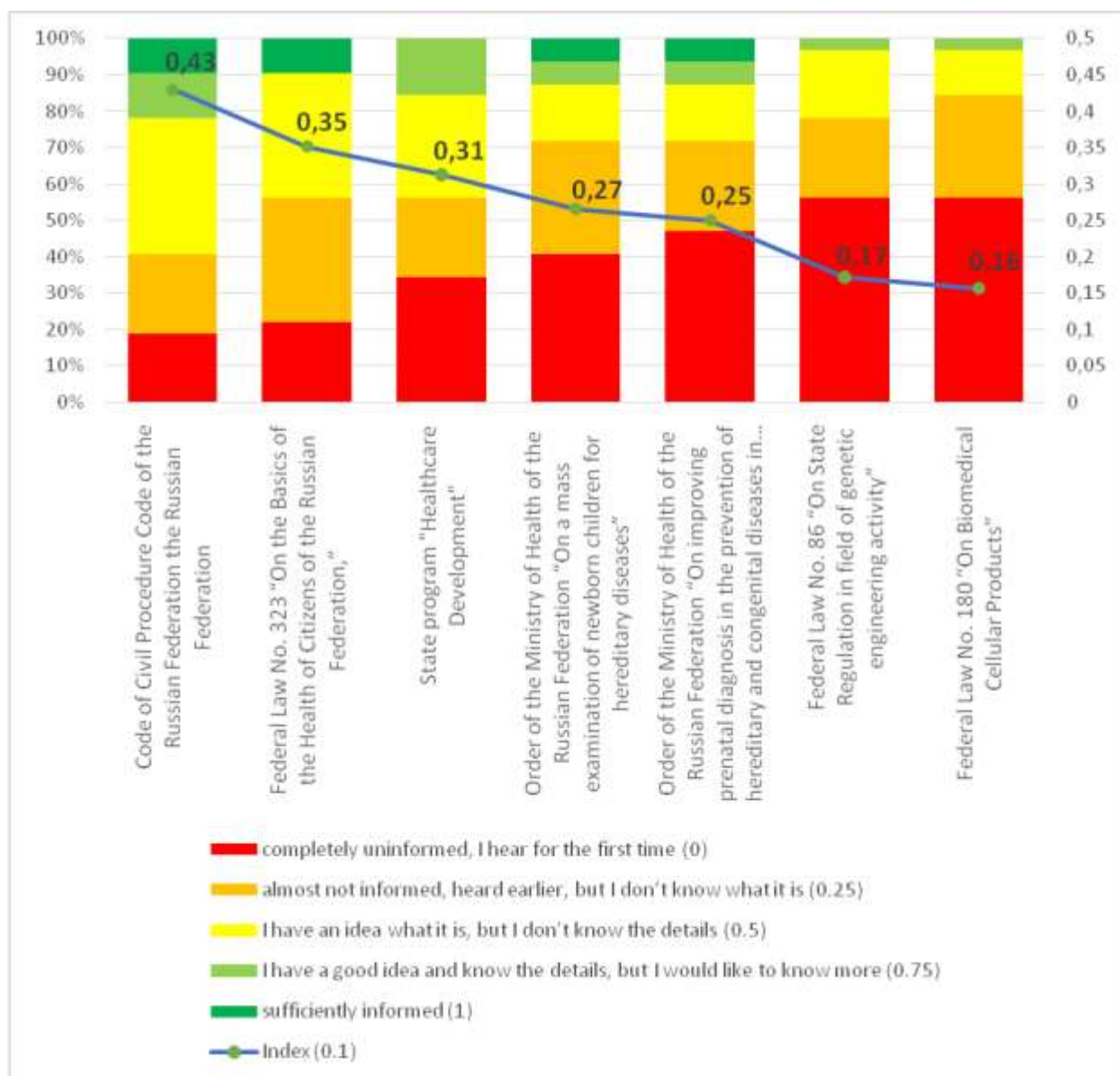


Figure 3: The degree of awareness regarding laws, codes, programs, orders (the percentage of the number of respondents)

Figure 3 reflects the degree of respondents' awareness of federal laws and orders governing the diagnosis and assistance to people with IEI—for the convenience of comparison, we calculated the awareness index from (0) (completely uninformed, I hear for the first time) to (1) (sufficiently informed). As follows from the figure, the level of awareness of almost all federal

laws and orders from the proposed list is low for informants. A few more respondents are familiar with the Civil Procedure Code of the Russian Federation, but especially bad—more than half of the informants just learned about this from our questionnaire, and respondents are familiar with Federal Law No. 180 “On Biomedical

Cellular Products” and Federal Law No. 86 “On State Regulation in field of genetic engineering activity.” Despite a superficial acquaintance with Federal Law No. 323, “On the Basics of the Health of Citizens of the Russian Federation,” it is this law that the majority (58.1%) of respondents intend to use to protect their rights. Some of them will refer to the orders of the Ministry of Health of the Russian Federation, “On improving prenatal diagnosis in the prevention of hereditary and congenital diseases in children” (38.7%) and “On a mass examination of newborn children for hereditary diseases” (29.0%), which the degree of familiarity with these orders as our results show that the vast majority of informants are very superficial (most either did not hear about such an order or only heard the name).

## CONCLUSION

The following conclusions can be drawn in the framework of the study of the legal regulation of assistance and social aspects of medical support for patients suffering from IEI-PID, as well as other orphan diseases.

First, it is necessary to expand the “federal list” of diseases by transferring diseases from the “regional list” into it in order to minimize funding problems, which often leads to the death of people.

Secondly, it is necessary to develop criteria for the inclusion of a disease in the “federal” and “regional” lists. As a basis, it is possible to take such criteria as the frequency of occurrence of the disease in the population, severity of the disease, and cost of the annual course of necessary drugs.

Thirdly, it is necessary to develop our own pharmaceutical industry in order to obtain high-quality domestic medicines (not analogues) with an adequate cost. Also, detailed regulatory requirements are required by the difficult issue of prescribing extremely expensive medications to patients of orphan diseases for health reasons.

Fourth, it is necessary to develop diagnostic medicine and increase the literacy of doctors regarding orphan diseases. Regarding the diagnosis of genetically caused diseases, it should be noted that currently in the Russian Federation there is a serious gap in the legal regulation of both genetic diagnostics and its varieties, including screening, which was confirmed by studies in which the authors of this article took part [13–15] and studies of other authors [16, 17].

Fifth, developments require federal standards for the provision of medical care to patients with IEI-PID, because at the level of subjects, including in the Sverdlovsk region, the first steps were taken in this direction. In particular, the routing of patients with IEI-PID was carried out—the scheme for providing medical care to patients with PID in need of supportive therapy was approved. The procedure for the formation, maintenance, and transfer of personalized registers of patients with IEI-PID was approved to provide them with drugs and specialized products (medical nutrition) at the expense of the regional budget, as well as a center for monitoring orphan diseases [18, 19].

The measures outlined above, when implemented together, should undoubtedly significantly improve the existing situation. In support of these arguments, we can give an example with the situation related to the legal regulation of the provision of cancer care in the sphere of which there

were similar problems in our country, but recently, according to experts, a positive qualitative shift has been outlined [20].

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