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CURRENT PROBLEMS AND ISSUES IN THE DIAGNOSIS OF ORPHAN DISEASES IN CHILDREN

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Abstract

The review provides current data on the definition and number of orphan diseases in general, around the world, and in individual countries. World data and a small amount of experience from our own research are presented, indicating that rare diseases are complex, chronic diseases that require an interdisciplinary approach, and create many problems for patients, families, clinicians, as well as society and governments. The relevance of lysosomal storage diseases is highlighted. Orphan diseases are characterized by many problems: late diagnosis, multiple visits to the doctor before diagnosis, misdiagnosis, low or no access to medications. The diagnostic odyssey presents the importance of neonatal screening, tandem mass spectrometry as the most effective method for screening, as well as whole exome and whole genome sequencing. The continuing medical, social, economic and other problems of orphan diseases indicate the need to expand international cooperation, create patient organizations and communities for doctors, train personnel in the field of laboratory and clinical genetics, and conduct basic scientific research.

Keywords: Orphan Diseases; Hereditary Metabolic Diseases, Lysosomal Storage Diseases, Neonatal Screening, Tandem Mass Spectrometry.

The problems of organizing and providing medical care to children with rare or orphan (orphan - orphan) diseases are of great relevance today [1, 13]. Rare diseases are diseases that occur in 1–1.3:2000 people [24, 91]. Orphan diseases include congenital (hereditary) or acquired diseases, the frequency of which in countries and the world does not exceed a certain number established by the legislation of various countries. At the same time, there is not a single generally accepted definition of rare diseases in the world. There are different national definitions of a “rare disease”: the prevalence of rare diseases varies from 5 to 80 per 100,000 [57]. In the Russian Federation, orphan diseases are those whose prevalence is no more than 10 cases per 100 thousand population [9]. In the USA, a disease is considered rare if it occurs in less than 200,000 (~ 1:1600) people [65]. In Europe, a rare disease is defined as one that affects fewer than five people in 10,000 [25, 73]. The United Kingdom has coined the terms “ultra-orphan drugs” and “ultra-rare diseases” to define conditions that affect fewer than 1,000 people across the UK [21]. Health Canada defines rare diseases as life-threatening, debilitating or serious and chronic conditions affecting a small number of people. Number of people (< 50 cases per 100,000 population) [16].

In Japan, any disease that affects fewer than 50,000 people in the country is considered rare, which corresponds to less than 1 in 2,500 people [48], in Korea, a disease is considered rare if it affects fewer than 20,000 patients or its prevalence is unknown due to rarity [44]. An

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estimated 300,000 people in Ireland live with one of more than 6000 known RDs [41]. The definition can also vary within one country: for example, in the Canadian province of Alberta, conditions are considered rare if they are registered in 1 in 50 thousand people, and in the province of Ontario - in 1 in 100–150 thousand people [22].

Currently, the scientific community knows of 6000–8000 rare diseases [62, 64], with another 250–280 new diseases described annually [83]. Two studies conducted by the Japan Medical Research and Development Agency estimated that the number of cases of rare and undiagnosed diseases was more than 37,000 [48]. In China, there are approximately 15.6 million people with rare diseases, which is a fairly large group [86]. All of the above once again demonstrates the relevance and scale of the problem of patients with rare diseases [10, 79].

According to the European Orphanet registry, information on 6,172 unique orphan diseases has been registered to date, 71.9% of which are genetic, the rest are the result of bacterial or viral infections, autoimmune or degenerative disorders. 69.9% of rare diseases have an onset exclusively in childhood [64, 88], with the majority (75%) manifesting during the first 5 years of life [14]. Many rare diseases are congenital and are detected at birth. More than 50% of rare diseases also affect adults. In 65% of cases they lead to disability, in 35% of cases they cause death in the first year of life, in 10% - before the age of 5 years, in 12% - between the ages of 5 and 15 years [95].

According to the Online Mendelian Inheritance in Man (OMIM) [94], as of August 2020, 9173 inherited diseases have been reported, of which 3308 are diseases classified as phenotypes of unknown molecular basis [48]. Orphan diseases affect all demographic groups of the population and, accordingly, all areas of medicine [61]. A disease may be rare in one region but common in another. This is a case of thalassemia, an anemia of genetic origin that is rare in northern Europe but common in the Mediterranean. “Periodic disease” is rare in France, but common in Armenia. There are also many common diseases whose variants are rare. The largest number of diseases with rare status are classified as oncology, oncohematology and neurology [90].

Although orphan diseases are rare by definition, it has been estimated that a rare disorder affects one in 16 people [29]. An Italian registry study found that rare diseases accounted for 4.2% of years of life lost in the general population, higher than the proportion of infectious diseases (1.2%) and diabetes (2.6%) [51]. According to a 2019 analysis, rare diseases affect a conservative estimate of 3.5% to 5.9% of the global population, equivalent to 263 to 446 million people worldwide [57]. A 2018 report provided a similar estimate of 350 to 400 million, or 3.5 million in the UK, meaning that approximately 1 in 17 people will have a rare disease at some point in their lives [37].

Thus, although rare diseases are individually rare, collectively they represent a significant burden. Between 2008 and 2018, rare disease patients under diagnosis cost the NHS in England more than £3.4 billion [37], highlighting unresolved challenges and inefficiencies.

Rare diseases are typically complex, serious, chronic and multisystem life-threatening illnesses, often associated with physical, sensory and intellectual disabilities. Rare diseases are

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often fatal and can have devastating consequences on length and quality of life, especially if the majority of rare diseases occur in childhood [26, 45]. Moreover, a study from an Italian registry found that rare diseases accounted for 4.2% of years of life lost in the general population, higher than the proportion of infectious diseases (1.2%) and diabetes (2.6%) [51].

Treatment is available for some rare diseases [43], but for most, only symptomatic treatment is possible. In many cases, patients require follow-up care from multiple health and social care professionals, requiring a high level of integrated care and coordination of services between clinic, community, social and primary care services [17, 89].

Lysosomal storage diseases

Hereditary metabolic diseases are the most complex and large group of diseases, errors in diagnosis of which are often encountered in pediatric practice. Hereditary metabolic diseases number about 800 diseases [96]. Their frequency, according to mass screening, is estimated at 1:1000 live births [71]. Among hereditary metabolic diseases, lysosomal storage diseases (LSDs), which include about 60 nosological forms, often leading to death at an early age, are of particular relevance. Increased attention to LBN is due, first of all, to the emerging possibilities of pathogenetic therapy using genetically engineered enzyme replacement drugs for the correction of metabolic disorders.

Lysosomal storage diseases (LSDs) are a group of rare diseases characterized by lysosomal enzyme deficiency, which results in the accumulation of substrate of the defective enzyme. Depending on the specific enzyme affected, different molecules will accumulate. In all cases, the accumulation causes lysosomal and cellular dysfunction per se, as well as activation of signaling pathways with additional deleterious long-term effects such as inflammatory pathways [60, 77]. LHDs are hereditary and debilitating metabolic disorders with a wide range of multiorgan clinical signs and symptoms (ranging from severe hydrops fetalis and early onset to mild, asymptomatic forms) that occur even in adults, which progress at varying rates [78]. The most pronounced changes extend to skeletal lesions, neuropathology, and visceral organomegaly.

Precisely identifying the molecular defect underlying rare diseases is not always easy. LPN was one of the first rare diseases in which the cause of the disease could be related to an enzyme change [72, 78]. A group of malfunctioning enzymes contained within the lysosome caused the appearance of LPN. The classification of LBN was based on the nature of the accumulated molecule due to the absence or reduction of enzymatic activity. For example, in Pompe disease there is an accumulation of glycogen, in mucopolysaccharidosis - mucopolysaccharides, and in Gaucher disease and Fabry disease - glycosphingolipids of various types [72]. Depending on the degree of reduction in enzymatic activity, the number and type of mutations, and other modifying factors that have yet to be identified, symptoms of the disease can occur in childhood or later in life with varying organ involvement and severity. Early identification of the pathological pathways involved has led to much greater scientific knowledge about these four LBDs compared to other orphan diseases. However, there is little information in the published literature on experiences with patients with LBP [85]. LPN occurs in 1 in 5000 live births and

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is usually detected in infancy, although prenatal diagnosis is possible [63]. The frequency of individual forms ranges from 1:40,000 to 1:1,000,000 and less frequently; the total incidence is 1:7000–1:8000 newborns. Some countries conduct mass screening for these diseases [80]. Enzyme replacement therapy (ERT) is an effective treatment for children with various types of LBD, including mucopolysaccharide diseases, Pompe disease, and Gaucher disease [15, 20, 31, 36, 39, 54]. Although the availability of ERT has improved survival and quality of life in patients with multiple LPNs, this treatment may be limited by several factors. First, ERT cannot eliminate the consequences of the disease that are already present at the time of treatment [12]. It is important to note that some patients with LPN develop complications such as hydrops fetalis before birth [75]. Second, ERT administered postnatally is unable to cross the blood-brain barrier, and hematopoietic stem cell transplantation (HSCT) for MPS I is the only standard therapy for these LBDs [32]. Third, patients receiving ERT may develop antienzyme antibodies because their immune system recognizes the recombinant protein as a foreign antigen [70]. Some patients require immunomodulation to tolerate ERT [20, 69].

Issues in diagnosing orphan diseases

Patients with orphan diseases face significant challenges in diagnosis and access to appropriate coordinated services, care and treatment [66]. Patients/service users and carers/supporters report that lack of care coordination is a major barrier to accessing timely interventions and has a major impact on health and well-being [27, 74]. In patients with rare diseases, diagnostic delays can range from months to decades, with an average of four to five years [50]. On average, patients with rare diseases receive three misdiagnoses and consult with five doctors before receiving an accurate diagnosis [55].

The lengthy diagnostic process, where some patients remain undiagnosed or misdiagnosed, can be mentally and emotionally draining for patients and their loved ones. Based on responses from the 2019–2020 H-Care Survey, the EURORDIS Rare Barometer Survey found that people with rare diseases rate their experience of care as average or poor, with a lower average score than people with chronic diseases [28]. The diagnostic odyssey that many patients with rare diseases face often has multiple causes: a nonspecific clinical presentation involving multiple organ systems that appear unrelated, a general lack of awareness and training of physicians regarding rare diseases, and a lack of standards. Diagnostic criteria, limited number of specialists, inconsistent movement of patients through the health care system leading to loss of information and increasing the likelihood of errors, and sometimes limited access to diagnostic tools [38, 42].

It is important to note that rare diseases do not always go undiagnosed, and undiagnosed diseases are not always hidden rare diseases. An undiagnosed patient may suffer from a rare disease, a more common disease with an atypical course, several concurrent diseases including psychosomatic disorders, or a completely new and uncharacterized disease. Patients with both undiagnosed and rare diseases require extensive interdisciplinary assessment, access to modern information resources and specialized diagnostic methods, including molecular genetics [53]. Rare disease centers throughout Germany therefore offer appointment hours for undiagnosed patients with or without suspected rare disease.

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Regarding the diagnostic process, diagnosis may be delayed if the patient has not yet been referred to an appropriate specialist. This may be caused by delays in primary health care due to lack of knowledge about rare diseases, as well as systemic problems due to lack of coordination, collaboration and adequate information sharing among multiple health care providers [38, 76, 84]. A difficult diagnosis is defined by an inconclusive phenotype and genomic profile, insufficient biomarkers, the presence of nonspecific but general symptoms, or the simultaneous existence of more than one disease. In this case, the patient may require special equipment and referral to an expert center or referral network. In the case of diagnostic impasse, all available tests have been performed by experts, and the patient and physicians may be faced with a new, as yet undescribed disease [38, 76, 82].

Early diagnosis and treatment of rare (orphan) diseases are not only a major economic problem (high cost of drug therapy), but also a medical and social one.

Due to the fact that many orphan diseases are congenital (hereditary) or acquired diseases, an important area is prenatal diagnosis of the fetus and neonatal screening of all newborns for the purpose of early detection of hereditary diseases. Prenatal diagnostics allows you to identify disorders in the development of the child in the first trimester of pregnancy. The introduction of mass screening of newborns for a number of diseases (in the Russian Federation - phenylketonuria, galactosemia, congenital hypothyroidism, cystic fibrosis and adrenogenital syndrome), as well as screening for lysosomal storage diseases, allows not only to diagnose the disease, but also to begin timely treatment before serious clinical manifestations appear [5].

Newborn screening (NBS) is one of the world's outstanding scientific advances and the most successful public health initiative to prevent disability and mortality. Neonatal screening, being a multifaceted set of activities, requires the constant participation and attention of a number of medical services [6].

The traditional newborn screening (NBS) program has a history of more than 50 years of development [49]. This is a successful public health program that is designed to provide early detection of severe diseases by identifying various biochemical parameters in heel blood samples from newborns.

The history of newborn screening began in the second half of the last century, when in 1962 R. MacCready and R. Guthrie organized testing of children for phenylketonuria (PKU), collecting filter paper forms with dried blood spots from every newborn in Massachusetts [3] . Guthrie R. in 1963 in the USA proposed a test for mass screening for galactosemia [33, 34]. Since 1973, in Canada, J. Dussault and C. Laberge have carried out mass screening of newborns for congenital hypothyroidism by determining the concentration of thyroxine in a drop of blood on filter paper using the radioimmunological method [23]. Developed in 1977 by Pang et al. The methodology for screening for 21-hydroxylase deficiency—adrenogenital syndrome (AGS)—by 1991 had spread to 29 countries around the world [2]. The immunoreactive trypsin test, introduced in 1979 in New Zealand, has been the basis of neonatal screening for cystic fibrosis (CF) in a number of countries for more than 20 years [4].

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Early identification, diagnosis, and intervention for severe inherited metabolic disorders have contributed to preventing mortality and improving the quality of life of children with fatal neonatal diseases [68].

Currently, the most commonly used screening method is the use of tandem mass spectrometry (TMS), which has the significant advantage of cost-effectiveness and high throughput, and significantly improves screening. Unlike other previously used methods, it can effectively detect more than 40 inherited metabolic diseases [46, 58, 59, 92]. Inherited metabolic diseases specifically refer to a type of genetic disease with various defects in metabolic function, most of which are single-gene genetic diseases. These include macromolecular metabolic disorders such as lysosomal accumulation and mitochondrial diseases. It also includes low molecular weight metabolic disorders involving amino acids, organic acids and fatty acids [30]. TMS is one of the most modern methods for analyzing compounds in micro-quantities of biomaterial and is used to diagnose three main groups of NBOs: metabolic disorders of amino acids, organic acids and defects in mitochondrial β-oxidation of fatty acids.

With the transformation of society, which includes advances in medical research and economic growth, an emphasis has been placed on prenatal and postnatal care services, and the demand for congenital disability prevention networks has increased. There is an urgent need to develop a comprehensive NBS program capable of detecting a larger number of diseases with high accuracy [47, 87]. It also aims to promote early screening, diagnosis and treatment and improve the quality of life of newborns. Next-generation sequencing (NGS) technology is used in newborn genetic screening (NBGS), which includes sequencing of a panel of disease-targeted gene packages, whole exome sequencing, and whole genome sequencing [81]. NBGS can functionally detect pathogenic genes of various diseases. This has significantly increased detection rates and has played a key role in moving away from screening for some diseases based on biochemical testing. NBGS has various limitations that may hinder its implementation, including difficulties in interpreting site variants, confidentiality of genetic information, higher cost, the possibility of missing some diseases that require biochemical identification, and the risk of drug overdose caused by increased incidence. [81]. The BabySeq exome sequencing project (Boston, USA), the NC NEXUS exome sequencing project (North Carolina, USA), the NBSeq project (California, USA) and the NESTS genetic screening project (Beijing, China) have been reported in the literature [11, 35, 40 , 52, 67, 93]. The results of these programs demonstrated that genetic screening can detect a wide range of diseases and specific variants that NBS cannot detect and confirm the real value of genetic screening. In addition, a detailed analysis of disease inclusion conditions for gene screening and results interpretation criteria was conducted [18, 19], which provided a solid basis for further exploration of clinical applications of NBGS.

Organization of medical and social assistance to children with orphan hereditary genetic diseases in Uzbekistan.

In Uzbekistan, the prenatal and neonatal screening program has been implemented since 1998. The birth and education of a healthy generation is one of the priority areas of state policy of the Republic of Uzbekistan. In this regard, the republic is implementing a set of national

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measures to improve the health of mothers and children, prevent disability with the development of specialized care for women and children.

Taking into account not only the medical, but also the social significance of the problem, Uzbekistan has been implementing measures aimed at preserving the gene pool of our country for 25 years. Republican and 13 regional screening centers have been organized in the republic, equipped with the necessary laboratory equipment, diagnostic devices, and qualified personnel.

Since 1998, the State program "Mother and Child Screening" has been implemented for the early detection of congenital and hereditary diseases in children, including premarital examination of persons entering into marriage, prenatal screening of pregnant women for congenital malformations and chromosomal syndromes of the fetus, as well as mass neonatal screening for congenital hypothyroidism and phenylketonuria with subsequent treatment and correction of identified disorders and diseases. Screening centers also carry out dispensary observation of patients identified during screening, providing them with free medications and special nutrition, as well as medical and genetic counseling for families burdened with congenital and hereditary pathologies to calculate the repeat risk of having a child with this disease. There are more than 200 prenatal diagnostic rooms in the country that perform primary ultrasound examinations of pregnant women, as well as 5 cytogenetic laboratories.

As can be seen from the table, in 2022, neonatal screening covered 3,663,718 (91.0%) newborns, 918 children were included in the risk group for congenital hypothyroidism, 200 children were included in the dispensary group, and the frequency was 1:3990. The risk group for phenylketonuria included 224 children, and the dispensary group included 56 children. The incidence of phenylketonuria was 1:16355. These indicators are comparable to the frequencies of other countries, Russia, China, Turkey, where neonatal screening is carried out.

Table: Main results of the screening program for congenital hypothyroidism and phenylketonuria in the Republic of Uzbekistan for the period 2018-2022

Nosology							Frequency
	2018	2019	2020	2021	2022	Total	
Congenital hypothyroidism	632829	760624	702338	825804	742123	**3 663 718**	
% coverage	89	100	87,8	97,4	80,1	**91,0**	
Identified patients	157	203	149	200	209	**918**	**1:3990**
Phenylketonuria	632829	760624	702338	825804	742123	**3 663 718**	
% coverage	89	100	87,8	97,4	80,1	**91,0**	
Identified patients	38	61	40	56	29	**224**	**1:16355**

The country has established a system for monitoring and treating children with these diseases. Currently, 1,686 children with congenital hypothyroidism are registered at the dispensary, who are provided with free thyroid medications, and 442 children with phenylketonuria receive therapeutic nutrition, allowing these children to develop according to their age.

In addition to immunofluorescence analysis for phenylketonuria and congenital hypothyroidism, selective screening is carried out using tandem mass spectrometry for 31 metabolic diseases (11 amino acids and 30 acylcarnitines). 31,590 newborns were examined,

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of which 44 (1:718) children were identified with hereditary metabolic diseases, of which organic aciduria - in 28 (1:1128), amino acid metabolism disorders - in 15 (1:2106) children, a defect in mitochondrial beta-oxidation fatty acids – in 1 (1:31590) child.

Over the past 5 years, Uzbekistan has paid much attention to organizing social and medical care for children with orphan hereditary genetic diseases. Thus, in 2019, Resolution of the President of the Republic of Uzbekistan No. PP-4440 "On measures to further improve medical and social care for children with rare (orphan) and other hereditary genetic diseases" was adopted, which regulates social benefits for children under 18 years of age with chronically progressive and life-threatening rare (orphan) diseases, regardless of the progression and extent of the disease; conducting selective screening of newborns and young children for 6 lysosomal storage diseases: Pompe disease, Gaucher disease, Fabry disease, Krabbe disease, Niemann-Pick disease (types A and B) and mucopolysaccharidosis type I; free provision of children with cystic fibrosis/cystic fibrosis, hemophilia, thalassemia, juvenile arthritis with systemic onset - orphan drugs (for children with cystic fibrosis - also special foods), with epidermolysis bullosa - medical products [7].

In 2021-2022, selective screening was carried out in 33,470 newborns and young children who had clinical signs of risk for the 6 listed lysosomal storage diseases.

Since the end of 2022, the implementation of the Decree of the President of the Republic of Uzbekistan PP-No. 217 "On measures to create a system for providing medical and social assistance and free delivery of medicines to sick children diagnosed with spinal muscular atrophy" has begun [8]. A Fund to support sick children diagnosed with spinal muscular atrophy has been created under the Ministry of Health of the Republic of Uzbekistan.

From 2024, it is planned to expand mass neonatal screening to include cystic fibrosis along with phenylketonuria and congenital hypothyroidism, as well as expand selective screening to 14 lysosomal storage diseases, covering up to 100,000 newborns and young children annually.

Summarizing the world data and a little experience from our own research, it should be noted that rare diseases are complex, chronic diseases that require an interdisciplinary approach, and create many problems for individuals, families, clinicians, communities and governments. Rare disease patients face many disease-related challenges.

Ranging from late diagnosis, multiple physician visits prior to diagnosis, misdiagnosis, lack of complete information provided at the time of diagnosis, poor coordination of care, inadequate transition from pediatric to adult care, low or no access to medications, and insufficient or knowledge, research and clinical trials.

All this requires expanding international cooperation, creating patient organizations and communities for doctors, training personnel in the field of laboratory and clinical genetics, conducting basic scientific research using modern information and communication technologies (telemedicine, artificial intelligence, etc.) and digitalization.

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