Review

UDC 616.24(441)-008.64-053.3-056.7-07+616-056.43+616.832.21-007.23
https://doi.org/10.56871/CmN-W.2026.34.95.001

Extended neonatal screening in the Russian Federation: characteristics of nozological forms

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For citation: Ivanov D.O., Lyazina L.V., Fedorova L.A. Extended neonatal screening in the Russian Federation: characteristics of nozological forms. *Children's Medicine of the North-West*. 2026;14(1):7–20. (In Russ.). https://doi.org/10.56871/CmN-W.2026.34.95.001.

Received: 19.11.2025 **Revised: 27.12.2025** **Accepted: 20.03.2026**

ABSTRACT. Neonatal screening is aimed at early preclinical detection of hereditary and congenital diseases in order to start treatment early, prevent early death and disability of children. In the Russian Federation since 2023 Newborn babies are examined for 36 hereditary and congenital diseases with an organizational division into two types of care: neonatal screening, including screening for 5 diseases, and extended neonatal screening, including screening for 31 diseases: aminoacidopathy, organic aciduria, disorders of beta-oxidation of fatty acids, primary immunodeficiency, spinal muscular atrophy. All newborns, without exception, are subject to screening. Capillary blood samples are taken from the newborn's heel at the age of 24–48 hours in a full-term baby and on the 7th day (144–168 hours) of life in a premature newborn. The time of screening tests is no more than 72 hours from the time of receipt of test forms in the laboratory. The diagnosis uses enzyme immunoassay, fluorimetric method, tandem mass spectrometry and molecular genetic methods. Diagnostic algorithms have been developed for each disease. If the pathology is confirmed, the child is prescribed pathogenetic therapy. The article contains a list of 36 nosological forms included in the neonatal screening program, and describes the clinical characteristics for each disease. A family in which a child with a hereditary disease is identified is indicated medical genetic counseling.

KEYWORDS: *neonatal screening, congenital hypothyroidism, cystic fibrosis, adrenogenital syndrome, galactosemia, biotinidase deficiency, expanded neonatal screening, aminoacidopathies, organic acidurias, disorders of fatty acid beta-oxidation, primary immunodeficiencies, spinal muscular atrophy*

Funding. This study was not supported by any external sources of funding.

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Обзор

https://doi.org/10.56871/CmN-W.2026.34.95.001

Расширенный неонатальный скрининг в Российской Федерации: характеристика нозологических форм

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Для цитирования: Иванов Д.О., Лязина Л.В., Федорова Л.А. Расширенный неонатальный скрининг в Российской Федерации: характеристика нозологических форм. *Children's Medicine of the North-West*. 2026;14(1):7–20. https://doi.org/10.56871/CmN-W.2026.34.95.001.

Поступила: 19.11.2025 **Одобрена: 27.12.2025** **Принята к печати: 20.03.2026**

РЕЗЮМЕ. Неонатальный скрининг нацелен на доклиническое выявление наследственных и врожденных заболеваний с целью раннего начала лечения, профилактики младенческой смерти и инвалидизации детей. В Российской Федерации с 2023 г. проводится обследование новорожденных на 36 наследственных и врожденных заболеваний с организационным разделением на два вида помощи: неонатальный скрининг, в который входит обследование на 5 заболеваний, и расширенный неонатальный скрининг, включающий обследование на 31 заболевание — аминоацидопатии, органические ацидурии, нарушения бета-окисления жирных кислот, первичные иммунодефициты, спинально-мышечную атрофию. Скринингу подлежат все без исключения новорожденные дети. Забор образцов капиллярной крови осуществляется из пятки новорожденного в возрасте 24–48 ч у доношенного и на 7-е сутки (144–168 ч) жизни у недоношенного новорожденного. Время проведения скрининговых исследований составляет не более 72 ч от времени поступления тест-бланков в лабораторию. В диагностике применяются иммуноферментный анализ, флуориметрический метод, тандемная масс-спектрометрия и молекулярно-генетические методы. Для каждого заболевания разработаны алгоритмы диагностики. При подтверждении патологии ребенку назначается патогенетическая терапия. В статье приведен перечень 36 нозологических форм, включенных в программу неонатального скрининга, и описаны клинические характеристики для каждого заболевания. Семье, в которой выявлен ребенок с наследственным заболеванием, показано медико-генетическое консультирование.

КЛЮЧЕВЫЕ СЛОВА: *неонатальный скрининг, врожденный гипотиреоз, муковисцидоз, адреногенитальный синдром, галактоземия, недостаточность биотинидазы, расширенный неонатальный скрининг, аминоацидопатии, органические ацидурии, нарушения бета-окисления жирных кислот, первичные иммунодефициты, спинально-мышечная атрофия*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

INTRODUCTION

Neonatal screening is designed to detect hereditary and congenital disorders before clinical symptoms appear, with the aim of initiating treatment early and preventing infant mortality and childhood disability. Mass screening of newborns for phenylketonuria began in the Russian Federation (RF) in 1985, and for congenital hypothyroidism in 1993. Additionally, since 2006, screening for cystic fibrosis, adrenogenital syndrome, and galactosemia has been implemented in the RF (Order of the Ministry of Health and Social Development of the RF No. 185 dated March 22, 2006, "On Mass Screening of Newborns for Hereditary Diseases"). Since 2023, the Russian Federation has been screening newborns for 36 hereditary and congenital diseases, with the program organized into two types of care: neonatal screening, which includes testing for 5 diseases, and expanded neonatal screening (ENS), which includes testing for 31 diseases: aminoacidopathies, organic acidurias, fatty acid oxidation disorders, primary immunodeficiencies, and spinal muscular atrophy. Currently, tests as part of neonatal screening (for congenital hypothyroidism, cystic fibrosis, adrenogenital syndrome, galactosemia, and biotinidase deficiency) are conducted in neonatal screening laboratories at regional institutions, primarily medical-genetic counseling centers (MGK). In the Russian Federation, 10 centers have been established to diagnose diseases within the framework of ENS. The main regulatory documents governing neonatal screening are Order No. 222n of the Ministry of Health of Russia dated April 17, 2025, "On the Approval of the Procedure for the Provision of Medical Care in the Field of 'Neonatology'," Order of the Ministry of Health of Russia No. 274n dated April 21, 2022, "On the Approval of the Procedure for the Provision of Medical Care to Patients with Congenital and/or Hereditary Diseases," and Order of the Ministry of Health of Russia No. 745n dated December 19, 2025, "On Amending Paragraph 10 of the Procedure for Providing Medical Care to Patients with Congenital and/or Hereditary Diseases, Approved by Order of the Ministry of Health of the Russian Federation No. 274n dated April 21, 2022," Directive of the Government of the Russian Federation No. 1510-r dated June 9, 2022 No. 1510-r "On the procurement by the Federal State Budgetary Institution 'Federal Center for Planning and Medication Provision for Citizens' of the Ministry of Health of Russia of medical equipment for the implementation of expanded neonatal screening" (as amended and supplemented), Order of the Ministry of Health of Russia No. 808n dated December 27, 2022, "On the Approval of Lists of Federal State Medical Organizations under the Jurisdiction of Constituent Entities of the Russian Federation That Conduct Expanded Neonatal Screening, as well as conducting confirmatory biochemical, and/or molecular genetic, and/or molecular cytogenetic diagnostics, and the constituent entities of the Russian Federation attached to them," Methodological Recommendations "Method for Obtaining a Dried Blood Spot on a Test Card for Clinical Laboratory Testing" (2022), developed by the Association of Medical Geneticists and the Russian Society of Neonatologists. The methodological recommendations are available on the website of the Federal State Budgetary Scientific Institution "Academician N.P. Bochkov Medical-Genetic Research Center," Regulations on information exchange between medical organizations during the conduct of neonatal and expanded neonatal screening. Information exchange as part of neonatal and expanded neonatal screening for hereditary diseases is carried out through the Newborn Registry (ENS) of the VIMIS "Akineo" system. This is a specialized, vertically integrated medical information system for "Obstetrics and Gynecology" and "Neonatology" of the Russian Ministry of Health. These regulations are available on the website of the Federal State Budgetary Institution "V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology, and Perinatology" of the Ministry of Health of Russia.

PROCEDURE FOR NEONATAL (EXPANDED NEONATAL) SCREENING FOR CONGENITAL AND/OR HEREDITARY DISEASES

All newborns, without exception, are required to undergo screening. Capillary blood samples are collected from the heel of a newborn at 24–48 hours of age for full-term newborns and on the 7th day (144–168 hours) of life for preterm neonates. Blood samples are collected onto two filter paper test forms: five blood spots are applied to one for neonatal screening, and three spots to the second for expanded neonatal screening. A referral form is filled out electronically, printed, and attached to the

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

test form. All test forms with blood samples are delivered to regional neonatal screening laboratories, where testing for five conditions is conducted as part of neonatal screening, and the shipment of test forms to designated centers for expanded neonatal screening is arranged. Screening tests are conducted within 72 hours after the test forms arrive at a laboratory. If a newborn is in a high-risk group, the MGC will call within 24 hours to schedule an appointment for blood sample collection for repeat screening or for biological material collection (blood, urine) for confirmatory diagnosis. A decision is made regarding the need for hospitalization, the prescription of therapy, and referral to a specialist in the relevant field. Confirmatory diagnostics for newborns with suspected hereditary diseases identified through expanded neonatal screening in all regions of the Russian Federation is conducted at the Federal State Budgetary Scientific Institution "Academician N.P. Bochkov Medical-Genetic Research Center" (Moscow), which serves as a reference center. Confirmatory testing takes no more than 10 working days. Diagnostic methods include enzyme-linked immunosorbent assay (ELISA), fluorimetry, tandem mass spectrometry, and molecular genetic methods. Diagnostic algorithms have been developed for each disease. Upon confirmation of a pathology, a child is prescribed pathogenetic therapy [1]. Medications are provided at the expense of regional and federal budgets, as well as through the "Circle of Kindness" State Foundation for Assistance to Children with Severe and Rare Diseases. Federal clinical guidelines have been developed for most nosological forms.

According to the results of the ENS Federal Program for 2024, more than 1,226,000 children were born in all constituent entities of the Russian Federation. Coverage by primary screening was approximately 99%. About 1.6% of those screened were identified as being at risk. During 2024, a diagnosis of a hereditary disease included in the screening was confirmed in 726 children, including 430 newborns with inherited metabolic disorders, 121 newborns with primary immunodeficiencies, and 175 newborns with spinal muscular atrophy[1] [2]. In the Russian Federation, starting in 2026, neonatal screening is planned to be expanded to include two hereditary diseases: aromatic acid decarboxylase deficiency and X-linked adrenoleukodystrophy.

DISORDERS DETECTED THROUGH NEONATAL SCREENING

Congenital hypothyroidism (ICD-10 codes: E03.0 Congenital hypothyroidism with diffuse goiter; E03.1 Congenital hypothyroidism without goiter)

In 80% of cases, the condition results from congenital abnormalities of the thyroid gland. During screening, the level of thyroid-stimulating hormone (TSH) is measured. If the TSH level exceeds the threshold, it is remeasured (retest). If the capillary blood TSH level exceeds 40 mU/L, treatment is initiated immediately, prior to receiving the retest results. The next step is to measure the levels of TSH and free T4 in venous blood. If congenital hypothyroidism is suspected, an endocrinologist performs the differential diagnosis of various forms of hypothyroidism and initiates hormone replacement therapy. In the absence of treatment, the primary clinical manifestations are delayed mental and physical development. The incidence of congenital hypothyroidism in the Russian Federation, based on neonatal screening results, is 1:3,600 [3].

Cystic fibrosis (ICD-10 code — E84.9 Cystic fibrosis, unspecified (cystic fibrosis))

Cystic fibrosis is a hereditary disease with an autosomal recessive pattern of inheritance. During screening, the level of immunoreactive trypsinogen (IRT) is determined. If the threshold value is exceeded, a retest is performed on the 21st–28th day of life, as IRT activity subsequently decreases. Confirmatory diagnostic methods include a sweat test and molecular genetic testing, which involves searching for pathogenic variants (mutations) in the *CFTR* gene. Main clinical manifestations include chronic diseases of the respiratory tract and gastrointestinal tract. In some cases, a child with cystic fibrosis may have an IRT level within the reference range at birth; therefore, if a characteristic clinical picture develops, cystic fibrosis must be ruled out by performing a sweat test and/or molecular genetic testing. Modern treatment may include the use of targeted therapy that affects the function of the mutant CFTR protein. The prevalence of cystic fibrosis in the Russian Federation is 1:7,400 [4].

[1] The results of the federal program for expanded neonatal screening for 2024 have been summarized. URL: https://medgen.ru/press-tcentr/novosti/podvedeny-itogi-federal-noi-programmy-rasshirennogo-neonatal-nogo-skrininga-za-2024-god/ (accessed: 11/10/2025).

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Congenital adrenal hyperplasia (adrenogenital syndrome) (ICD-10 codes — E25.0 Adrenogenital disorders associated with enzyme deficiency; E25.9 Adrenogenital disorder, unspecified)

Congenital adrenal hyperplasia is a group of inherited disorders with an autosomal recessive pattern of inheritance associated with impaired steroidogenesis. The most common form (over 90% of cases) is 21-hydroxylase deficiency. During screening, the level of 17-hydroxyprogesterone (17-OHP) is measured. Screening is aimed at detecting the classic forms of congenital adrenal hyperplasia, namely salt-wasting and virilizing ones. In some cases, a non-classic form may be detected. Newborns with 17-OHP levels above the threshold value undergo retesting. Differential diagnosis and hormone replacement therapy are performed by an endocrinologist. Confirmatory diagnosis involves hormonal testing and molecular genetic testing to identify pathogenic variants (mutations) in the *CYP21A2* gene. The incidence of classic forms of adrenogenital syndrome based on neonatal screening results in the Russian Federation is 1:9,638 (ranging from 1:6,749 to 1:14,876 across different regions of the Russian Federation) [5].

Galactosemia (galactose metabolism disorder) (ICD-10 code — E74.2 Galactose metabolism disorder)

Galactosemia is a group of inherited disorders with an autosomal recessive pattern of inheritance. Total galactose levels are measured in the blood of newborns. Mutations in three genes (*GALT, GALK1, GALE*) lead to a deficiency of various enzymes (galactose-1-phosphaturidyltransferase, galactokinase, uridine diphosphate, galactose-4-epimerase) with the biochemical manifestation of galactosemia. The primary condition in the Russian population is type I galactosemia with galactose-1-phosphate uridyltransferase deficiency. If the total galactose level exceeds the threshold, a retest is performed. If a total galactose level above 15 mg/dL is detected in a newborn, immediate dietary intervention and hospitalization are recommended pending the retest results. In the absence of treatment, the classic form of type I galactosemia leads to liver damage progressing to hepatic cell failure and sepsis, which may be fatal. Lifelong treatment is based on an elimination diet that excludes galactose-containing foods (in newborns, this includes breast milk and infant formulas containing galactose or lactose). The confirmatory diagnostic workup includes measurement of galactose-1-phosphate uridyltransferase (*GALT*) enzyme levels and molecular genetic testing to identify pathogenic variants (mutations) in the *GALT* gene and other genes associated with galactosemia. Very often, a slight elevation of galactose in a newborn is associated with polymorphic variants in the *GALT* gene, where enzyme activity may decrease to 25% of normal, the so-called Duarte variant. In the Duarte variant, a decrease in total blood galactose levels is observed over time, with normalization occurring when the infant is fed breast milk or infant formula.In some cases, a diet restricting lactose intake is prescribed for the Duarte variant until blood galactose levels normalize. Patients with galactosemia are monitored by pediatricians, gastroenterologists, and geneticists. Starting in 2023, blood sampling in full-term newborns is performed within the first 24–48 hours, when galactose may not yet have accumulated in the blood to a clinically significant level. If galactosemia is suspected based on the clinical presentation in a child with normal galactose levels according to neonatal screening results, it is recommended to repeat the blood galactose test. In the Russian Federation, based on neonatal screening results, the incidence of galactosemia is 1:20,000 (including the Duarte variant) [6].

Biotinidase deficiency (ICD-10 code — E56.8 Deficiency of other specified B vitamins (biotinidase deficiency))

Biotinidase deficiency (biotin-dependent carboxylase deficiency) is an inherited disorder with an autosomal recessive pattern of inheritance. Biotinidase enzyme activity is measured in newborns. Confirmatory diagnosis involves measuring biotinidase activity in blood serum and molecular genetic testing to identify pathogenic variants (mutations) in the *BTD* gene. The main clinical manifestations are neurological (seizures, muscular hypotonia, psychomotor developmental delay) and cutaneous (seborrhea, atopic dermatitis, hair loss or poor hair growth, conjunctivitis). In the absence of timely treatment, children with very low enzyme activity develop irreversible severe mental retardation. Preclinical administration of biotin (the primary method of lifelong treatment) promotes normal child development. The global incidence is 1:40,000–1:60,000 [7].

DISEASES DETECTED THROUGH EXPANDED NEONATAL SCREENING

Amino acid metabolism disorders (E70 Disorders of aromatic amino acid metabolism)

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

A group of inherited disorders with an autosomal recessive pattern of inheritance. Diagnostic method: tandem mass spectrometry (TMS technology, which allows determining the concentrations of various markers for a large number of diseases in a single analysis). Clinically, the disease ranges from mild to severe forms, with classic clinical manifestations in the neonatal and early childhood periods.

Hyperphenylalaninemia (classical phenylketonuria, other types of hyperphenylalaninemia) (ICD-10 codes — E70.0 Disorders of aromatic amino acid metabolism (phenylketonuria); E70.1 Other types of hyperphenylalaninemia (deficiency of biopterin (tetrahydrobiopterin) synthesis, biopterin (tetrahydrobiopterin)

Blood samples from newborns are tested for levels of phenylalanine. If the result is above the threshold, a retest is performed. Confirmatory diagnosis includes determining elevated phenylalanine levels and the phenylalanine/tyrosine ratio prior to dietary therapy, as well as molecular genetic testing to identify pathogenic variants (mutations) in the *PAH* gene and the genes encoding cofactors for the enzyme phenylalanine hydroxylase (*PTS, QDRP, PCBD, GCHI, SPR, DNAJC12*). The most common form is classic phenylketonuria (98% of cases) with mutations in the *PAH* gene. By crossing the blood-brain barrier, phenylalanine breakdown products exert a toxic effect on brain cell metabolism, leading to mental retardation if left untreated.

Treatment for classic phenylketonuria is based on a lifelong diet that restricts phenylalanine intake when its level exceeds 360 μmol/L, along with the use of specialized medical foods that do not contain phenylalanine.

When diagnosing forms of biopterin (tetrahydrobiopterin) synthesis and reactivation deficiency, pathogenetic drug therapy is prescribed using a synthetic analogue of tetrahydrobiopterin (saproterin dihydrochloride) and serotonin precursors (levodopa preparations in combination with carbidopa). Patients with phenylketonuria are primarily monitored by geneticists and pediatricians. The incidence of hyperphenylalaninemia in the Russian Federation, according to neonatal screening data, is 1:7,000 (ranging from 1:4,735 to 1:18,000 across different regions) [8]. New methods of drug treatment for classic phenylketonuria are being developed and implemented worldwide, including in Russia.

Tyrosinemia, type I (tyrosine metabolism disorders) (ICD-10 code — E70.2 Tyrosine metabolism disorders (tyrosinemia)

Concentrations of tyrosine and succinylacetone are measured in blood. If succinylacetone and tyrosine levels exceed the threshold values, a retest is performed. An elevated level of succinylacetone is pathognomonic for type I tyrosinemia. Elevated tyrosine levels are observed in other types of hereditary tyrosinemia and in hepatopathies of other etiologies. The main clinical manifestations include impaired liver and kidney function, neurological symptoms, and rickets-like skeletal changes. Confirmatory diagnosis involves measuring elevated levels of succinylacetone in blood and urine, as well as molecular genetic testing to identify pathogenic variants (mutations) in the *FAH* gene. The mainstay of treatment for type I tyrosinemia is lifelong medication with nitizinone and a diet restricting phenylalanine and tyrosine intake, with the use of specialized medical foods that do not contain phenylalanine or tyrosine. Follow-up is conducted by a pediatrician and a geneticist. The incidence of type I tyrosinemia in various populations ranges from 1:100,000 to 1:120,000. The incidence in the Chechen Republic is 1:16,020 [9].

Leucinemia (maple syrup urine disease) (ICD-10 code — E71.0 Maple syrup urine disease)

The concentration of leucine (Leu/Ile/Pro-OH-leucine/isoleucine/hydroxyproline; amino acids are not separated in the analysis and appear as a single peak) is determined in the blood of a newborn. If leucine levels exceed the threshold, a retest and analysis of organic acids in urine are performed before initiating therapy. If leucine levels exceed 600 μM/L, hospitalization and a low-protein diet are recommended. Mutations in the *BCKDHA, BCKDHB, DBT, DLDA*, and *PPM1K* genes lead to a deficiency of branched-chain ketone acid dehydrogenase (a multi-enzyme complex), which is accompanied by metabolic disturbances and accumulation of the amino acids leucine, isoleucine, valine, and their derivatives. Confirmatory diagnosis involves elevated levels of leucine, isoleucine, and valine in the blood; elevated levels of 2-oxo-isocaproic, 2-hydroxy-isocaproic, 2-oxo-3-methylvaleric, 2-oxo-isovaleric, 2-hydroxyisovaleric, and 2-hydroxy-3-methylvaleric acids in urine; molecular genetic testing to identify pathogenic variants in the *BCKDHA, BCKDHB, DBT, DLDA*, and *PPM1K* genes.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

The main clinical manifestation in the classic course of leucinosis is acute infantile encephalopathy (generalized seizures, hyperexcitability, muscle hypertonia, alternating with lethargy, muscle hypotonia, and impaired consciousness up to coma) with a potentially fatal outcome.

The basis of treatment is a diet restricting foods rich in leucine, isoleucine, and valine, and the use of specialized therapeutic foods that do not contain leucine, isoleucine, or valine. Drug therapy includes the administration of L-carnitine and thiamine. Hospitalization is indicated in case of metabolic crisis. Monitoring is carried out by a pediatrician, a neurologist, and a geneticist. The global incidence is 1 in 185,000 [10].

Homocystinuria (disorders of sulfur-containing amino acid metabolism) (ICD-10 code — E72.1 Disorders of sulfur-containing amino acid metabolism (homocystinuria))

Methionine concentration is measured in blood samples.

1. Screening is primarily aimed at diagnosing the classic form of homocystinuria associated with cystathionine β-synthase deficiency. Inhibition of the enzyme at the level of further homocysteine metabolism leads to its accumulation and, consequently, to the accumulation of methionine as a precursor. If the methionine level exceeds the threshold value, a retest is performed. Confirmatory diagnosis involves the detection of elevated levels of methionine and homocysteine in blood plasma (and homocystine in urine), as well as molecular genetic testing to identify pathogenic variants (mutations) in the *CBS* gene. The main manifestations are mental retardation with clinical signs of connective tissue dysplasia, including tall stature, thrombosis, and cardiovascular pathology. Treatment involves a diet restricting foods rich in methionine and the use of a specialized medical food product that does not contain methionine. A trial treatment with pyridoxine allows for identifying B_6-dependent and B6-resistant forms of homocystinuria, followed by treatment with pyridoxine for the B_6-dependent form of homocystinuria. Elevated blood methionine levels are also observed in liver diseases and other hereditary disorders.

2. A retest is performed if the methionine level in a newborn is below the threshold value. If the methionine level remains below the threshold, hereditary conditions associated with both methylenetetrahydrofolate reductase (*MTHFR*) deficiency and cobalamin metabolism disorders must be ruled out (tandem mass spectrometry shows an increased level of C3 (propionylcarnitine), as well as there is an increase in the level of methylmalonic acid in the urine). Mutations in the *MTHFR* gene lead to a deficiency of methylenetetrahydrofolate reductase, which is involved in converting (remethylation) homocysteine to methionine, resulting in methionine deficiency. Key clinical symptoms include muscle hypotonia, delayed psychomotor development, neurological disorders, microcephaly, and megaloblastic anemia (in certain forms of cobalamin metabolism disorders). Confirmatory diagnosis of homocystinuria with impaired homocysteine remethylation includes measurement of homocysteine levels in blood and urine, analysis of urinary organic acids, and molecular genetic testing of genes associated with non-classical homocystinuria (*MTR, MTRR, MMADHC, PRDX1, LMBRD1, ABCD4*). Medication therapy is based on betaine, which helps lower homocysteine levels by converting it back into methionine and dimethylglycine, followed by breakdown. Betaine is also prescribed for the classic form of homocystinuria. In some cases, children with homocystinuria, whether classic or with methylation defects, have normal methionine levels based on neonatal screening results; therefore, blood homocysteine testing is required when a characteristic clinical picture is present. These children are monitored by a pediatrician, a neurologist, and a geneticist. The global prevalence of classic homocystinuria is 1:100,000–1:200,000 [11].

Citrullinemia, type I (disorders of the urea cycle) (ICD-10 code — E72.2 Disorders of the urea cycle (citrullinemia, type I))

Citrulline levels are measured in blood. If citrulline levels exceed the threshold value, a retest and analysis of urinary organic acids are performed before initiating therapy. If citrulline levels are elevated (>80 μmol/L), a low-protein diet is prescribed and hospitalization is recommended. Lack of the argininosuccinate synthetase, which is involved in the urea cycle, leads to hyperammonemia with a clinical picture of acute encephalopathy following a period of "clear interval," rapid progression of neurological deficits up to neonatal coma and cerebral edema with a potentially fatal outcome. Confirmatory diagnosis includes elevated citrulline levels, ammonia level testing (hyperammonemia), urinary organic acid

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

analysis (increased orotic acid excretion), and molecular genetic testing to identify pathogenic variants (mutations) in the *ASS* gene. Treatment includes a low-protein diet, maintaining caloric intake, administration of vitamins and minerals via specialized medical nutrition products, and prescription of L-arginine and medications that lower blood ammonia levels. Extracorporeal detoxification methods and liver transplantation are also used. The global prevalence is 1–9 per 100,000 [1, 12].

Argininosuccinic aciduria (argininosuccinate lyase deficiency) (ICD-10 code — E72.2 Disorders of the urea cycle (argininosuccinate lyase deficiency))

Arginine succinate (Asa) concentrations are measured in blood. If the level exceeds the threshold value, a retest and analysis of urinary organic acids are performed before initiating therapy. If the Asa concentration is >1.5 μmol/L, a low-protein diet and hospitalization are recommended. An acute deficiency of the enzyme argininosuccinate lyase, which is involved in the urea cycle, leads to hyperammonemia with a clinical picture of acute encephalopathy following a "clear interval," rapid progression of neurological disorders up to neonatal coma, cerebral edema with a potentially fatal outcome. Confirmatory diagnosis includes elevated levels of argininosuccinic acid and citrulline in the blood, ammonia level testing (hyperammonemia), urinary organic acid analysis (elevated excretion of argininosuccinic acid), and molecular genetic testing to identify pathogenic variants (mutations) in the *ASL* gene. Treatment is similar to that for type I citrullinemia. The global incidence is 1:70,000–1:91,000 [1, 12].

Argininemia (urea cycle disorders) (ICD-10 code — E72.2 Urea cycle disorders (arginase deficiency))

Arginine concentration is measured in blood. If the arginine level exceeds the threshold value, a retest and analysis of organic acids in the urine are performed before initiating therapy. Deficiency of arginase, which is involved in the urea cycle, leads to hyperammonemia with clinical manifestations of vomiting, anorexia, restlessness, and crying in infants. Acute encephalopathy is less common. Older children may exhibit delayed speech and language development, epilepsy, neurological symptoms. Confirmatory diagnosis includes elevated blood arginine levels, analysis of urinary organic acids (frequently elevated orotic acid excretion), and molecular genetic testing to identify pathogenic variants (mutations) in the *ARG1* gene. Treatment consists of a low-protein diet with minimal arginine content, maintenance of caloric intake, vitamins, and minerals using specialized therapeutic foods, and administration of medications that lower blood ammonia levels in cases of hyperammonemia. The global prevalence is 1 in 353,000 [1, 12].

Organic acidurias

Organic acidurias are a group of inherited disorders with an autosomal recessive pattern of inheritance. The diagnostic method is TMS. To detect organic acidemias (acidurias), acylcarnitine concentrations are measured. Due to gene mutations, an enzyme block occurs, leading to a buildup of organic compounds and their derivatives, which exert a toxic effect on the cell metabolism, central nervous system, liver, and other organs. The biochemical pathway is disrupted, leading to a reduction in subsequent metabolites involved in vital bodily processes, such as gluconeogenesis. These conditions are characterized by varying times of onset, with the most severe course occurring in the neonatal period.

Propionic acidemia (ICD-10 code — E71.1 Other disorders of branched-chain amino acid metabolism (propionic acidemia)) [13]

Methylmalonic acidemia (ICD-10 code — E71.1 Other disorders of branched-chain amino acid metabolism (methylmalonic acidemia/aciduria (methylmalonyl-CoA mutase deficiency)); methylmalonic acidemia (cobalamin A deficiency); methylmalonic acidemia (cobalamin B deficiency); methylmalonic acidemia (methylmalonyl-CoA epimerase deficiency); methylmalonic acidemia (cobalamin D deficiency); methylmalonic acidemia (cobalamin C deficiency).

C3 (propionylcarnitine) concentration and the C3/C2 ratio are measured in blood samples. If their levels exceed the threshold value, a retest is performed. Differential and confirmatory diagnosis of propionic, methylmalonic acidemias, and disorders of cobalamin synthesis (combination of methylmalonic acidemia with non-classical homocystinuria) is performed through the analysis of urinary organic acids (increased excretion of propionic or methylmalonic acids, respectively, as well as 3-hydroxypropionic, 3-hydroxy-n-valeric acids, and methylcitrate), blood and urine homocysteine testing, and molecular genetic diagnosis to identify pathogenic variants (mutations) in the *PCCA, PCCB,*

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MCEE, MMAA, MMAB, MMACHC, MMADHC, PRDX1, LMBRD1, ABCD4, CD320. A slight elevation in C3 may be associated with vitamin B12 deficiency. Clinically, acidemias manifest as feeding difficulties, muscle hypotonia, psychomotor developmental delay, and metabolic crises with a potentially fatal outcome. The mainstay of treatment (except for cobalamin C and D deficiency) is a low-protein diet supplemented with specialized medical foods that do not contain isoleucine, valine, threonine, or methionine. Carnitine, metronidazole, and medications that lower ammonia levels are prescribed; biotin and vitamin B_{12} are prescribed as indicated. In cases of cobalamin deficiency, vitamin B_{12} is prescribed at a dose of 1–5 mg/day (hydroxocobalamin, adenosylcobalamin); betaine and folic acid are also prescribed for cobalamin C and D deficiency. Patients are monitored by a pediatrician, a neurologist, and a geneticist. The global prevalence of methylmalonic acidemia is 1:50,000, and the prevalence of propionic acidemia is 1:350,000 [14].

Isovaleric acidemia (ICD-10 code — E71.1 Other disorders of branched-chain amino acid metabolism (isovaleric acidemia))

The concentration of C5 (isovalerylcarnitine) is measured in blood. If the C5 level exceeds the threshold, a retest and an analysis of urinary organic acids are performed before initiating therapy. Confirmatory diagnosis involves urine organic acid analysis (elevated levels of isovaleric acid, 3-hydroxyisovaleric acid, and isovalerylglycine) and molecular genetic testing to identify pathogenic variants (mutations) in the *IVD* gene. Clinically, the disease ranges from asymptomatic to severe, presenting as acute infantile encephalopathy with severe ketoacidosis and a potentially fatal outcome. An unusual “sweaty feet” odor in the urine is typical. Treatment is based on a low-protein diet supplemented with specialized therapeutic foods that do not contain leucine. L-carnitine, glycine, and medications that lower ammonia levels are prescribed. Metabolic crisis must be managed. These patients are not prescribed medications containing benzoic or salicylic acid due to competition with isovaleryl-CoA for conjugation with glycine. Children are monitored by a pediatrician, a neurologist, and a geneticist. The global incidence is 1:60,000–1:150,000 [15].

3-hydroxy-3-methylglutaric acid deficiency (ICD-10 code — E71.1 Other disorders of branched-chain amino acid metabolism (3-hydroxy-3-methylglutaric acid deficiency))

The concentration of C_5OH (3-hydroxyisovalerylcarnitine) is measured in blood. A C_5OH level above the threshold is also observed in biotinidase deficiency, holocarboxylase synthetase deficiency, and 3-methylcrotonyl-CoA carboxylase deficiency. Differential and confirmatory diagnosis includes determination of biotinidase activity, analysis of urinary organic acids (elevated levels of 3-hydroxy-3-methylglutaric, 3-methylglutaric, 3-methylglutaconic, 3-hydroxyisovaleric, 3-methylglutarylglycine, methyl-crotonylglycine), and molecular genetic testing to identify pathogenic variants (mutations) in the *HMGCL* gene. Clinically, the condition is characterized by neurological symptoms, metabolic crises (metabolic acidosis, hypoketotic hypoglycemia), and a Reye-like syndrome. Treatment is based on a low-protein diet and therapeutic foods that do not contain leucine. Fat intake is restricted. Carnitine is prescribed. Metabolic crises are managed. Patients are monitored by a pediatrician, a neurologist, and a geneticist. The global incidence is 1 in 1,000,000 [16].

Beta-ketothiolase deficiency (ICD-10 code — E71.1 Other disorders of branched-chain amino acid metabolism (beta-ketothiolase deficiency))

Concentrations of C5:1 (tiglilcarnitine) and C_5OH (3-hydroxyisovalerylcarnitine) are measured in blood. If the C5:1 level exceeds the threshold, a retest is performed. Confirmatory diagnosis includes: elevated C5:1 and C_5OH levels in the blood, analysis of urinary organic acids (elevated tiglylglycine, 2-methyl-3-hydroxybutyrate, and 2-methylacetoacetate), and molecular genetic testing, namely searching for mutations in the *ACAT1* gene. Episodes of ketoacidosis, triggered by fasting, stress, or intercurrent illnesses, are common. Clinically, symptoms include vomiting, muscle hypotonia, shortness of breath, seizures, impaired consciousness, delayed motor and mental development, and motor disorders. The basis of treatment is a low-protein diet, restriction of fat intake; frequent meals; increased carbohydrate intake; and administration of carnitine in cases of free carnitine (C0) deficiency. Children are monitored by a pediatrician, a neurologist, and a geneticist. The global prevalence is 1 in 1,000,000 [1, 14].

Glutaric acidemia, type I (ICD-10 code — E72.3 Disorders of lysine and hydroxylysine metabolism (glutaric acidemia, type I))

The concentration of C5DC (glutaric acid) is measured in blood. If the C5DC level is above the threshold, a retest and an analysis of urinary

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organic acids are performed before starting therapy. Confirmatory diagnosis involves testing for organic acids in urine (elevated levels of glutamic and 3-hydroxyglutamic acids) and molecular genetic testing to identify pathogenic variants (mutations) in the *GCDH* gene. Clinically, the condition is characterized by macrocephaly, encephalitis-like seizures, neurological symptoms, and a spastic-hyperkinetic pattern of cerebral palsy. The basis of treatment is a diet restricting foods rich in lysine and tryptophan, along with specialized therapeutic foods that do not contain lysine or tryptophan. Levocarnitine is prescribed. Patients are monitored by a pediatrician, a neurologist, and a geneticist. In 5% of cases, when a child has type I glutaric aciduria, the C5DC concentration is within normal limits according to neonatal screening results; therefore, if the disease is clinically suspected, urine organic acid analysis and molecular genetic testing are performed. Elevated C5DC levels are observed in type II glutaric aciduria and kidney diseases. The prevalence in Western European countries is 1:30,000–1:100,000. In the Russian Federation, the prevalence of the disease has not been determined [17] and will be clarified upon implementation of the newborn screening program.

Holocarboxylase synthetase deficiency (biotin-sensitive multiple carboxylase deficiency) (ICD-10 code — E56.8 Deficiency of other specified B vitamins (holocarboxylase synthetase deficiency))

C_5OH (3-hydroxyisovalerylcarnitine) concentration is measured in blood. Elevated C_5OH levels are also observed in biotinidase deficiency and other metabolic disorders. Differential and confirmatory diagnosis includes: determination of biotinidase activity, analysis of urinary organic acids (elevated levels of β-hydroxyisovaleric, β-hydroxypropionic, fumaric, and 2-ketoglutaric acids, 3-methylcrotonylglycine, methylcitrate, and tiglylglycine), and molecular genetic diagnosis to identify pathogenic variants (mutations) in the *HLCS* gene. Clinically, the condition is characterized by neurological manifestations (seizures, muscle hypotonia, impaired consciousness), mental retardation, motor delay, dermatitis, and metabolic acidosis. Primary treatment involves the administration of biotin and L-carnitine, as well as correction of metabolic acidosis. The global prevalence is 1:200,000. The prevalence in the Russian Federation has not yet been established [1, 7, 18].

Fatty acid beta-oxidation disorders (ICD-10 code — E71.3 Fatty acid metabolism disorder)

Fatty acid beta-oxidation disorders are hereditary diseases with an autosomal recessive pattern of inheritance. Diagnostic method: TMS. To diagnose organic acidurias, acylcarnitine concentrations are measured. If there is an initial deviation from the acylcarnitine threshold level, a retest is performed. Confirmatory diagnosis includes characteristic TMS acylcarnitine spectrum profiles, urinary organic acids, and molecular genetic testing. The main clinical manifestations are muscle hypotonia and weakness, ketotic hypoglycemia, metabolic crises, dicarboxylic aciduria, Reye-like syndrome. Treatment is lifelong. Patients are monitored by a pediatrician, a neurologist, and a geneticist [19]. The prevalence of nosological forms of fatty acid β-oxidation disorders in the Russian Federation will be clarified based on the results of the ENS Program.

Primary carnitine deficiency (ICD-10 code — E71.3 Fatty acid metabolism disorder (primary carnitine deficiency))

A decrease in C0 (free carnitine) concentration is observed. The disease is caused by mutations in the *SLC22A5* gene. Primary treatment consists of levocarnitine at an average dose of 100 mg/kg per day (50–400 mg/kg), with correction during a metabolic crisis. The global incidence is 1:20,000–1:70,000.

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) (ICD-10 code — E71.3 Fatty acid metabolism disorder (medium-chain acyl-CoA dehydrogenase deficiency))

Elevated concentrations of medium-chain acylcarnitines are detected: C8 (octanoylcarnitine), C6 (hexanoylcarnitine), C10 (decanoylcarnitine), and C10:1 (decenylcarnitine), as well as the C8/C10 and C8/C2 ratios. The disorder is caused by mutations in the *ACADM* gene. Primary treatment involves avoiding fasting to prevent hypoglycemic episodes, eating every 3–6 hours for children over 1 year of age. Infants under 1 year old should eat more frequently. If C0 is low, carnitine should be prescribed. Metabolic crisis requires immediate intervention. The incidence in Europe and the U.S. is 1:8,300–1:15,000.

Long-chain acetyl-CoA dehydrogenase deficiency (mitochondrial trifunctional protein (TFP) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHADD) deficiency) (ICD-10 code — E71.3 Fatty acid metabolism disorder (long-chain acyl-CoA dehydrogenase deficiency))

Elevated concentrations of acylcarnitines are detected, including C18OH (3-hydroxy-octadecanoylcarnitine), C18:1OH (3-hydroxy-octadecenoic acid carnitine), C16OH (3-hydroxy-hexadecanoic

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acid carnitine), C16:1OH (3-hydroxy-hexadecenoic acid carnitine). Levels of C0 (free carnitine) are decreased. the disorder is caused by mutations in the *HADHA* gene. Primary treatment includes frequent meals. Breaks should not exceed 3–6 hours during the day and 3–8 hours at night, depending on age. A diet should limit foods rich in long-chain fatty acids and include specialized medical foods containing medium-chain fatty acids. Valproic acid is not recommended in cases of concomitant conditions. The global prevalence is 1 in 300,000.

Very-long-chain acetyl-CoA dehydrogenase deficiency (VLCADD) (ICD-10 code — E71.3 Fatty acid metabolism disorder (very-long-chain acetyl-CoA dehydrogenase deficiency))

Elevated concentrations of acylcarnitines C14:1 (tetradecenoic acid carnitine), C14 (tetradecanoic acid carnitine), C14:2 (tetradecadienoic acid carnitine), C16:1 (hexadecenoic carnitine), and the C14:1/C16 ratio are identified. The disorder is caused by mutations in the *ACADVL* gene. Elevated levels of these metabolites are observed in heterozygous carriers of the ACADV gene in clinically healthy individuals. The main treatment is similar to long-chain acetyl-CoA dehydrogenase deficiency. The global prevalence is 1:30,000–1:100,000.

Carnitine palmitoyltransferase deficiency, type I (ICD-10 code — E71.3 Fatty acid metabolism disorder (carnitine palmitoyltransferase deficiency, type I))

Elevated concentrations of C0 (free carnitine) and the C0/(C16+C18) ratio, as well as decreased concentrations of C16 (hexadecanoylcarnitine) and C18 (stearoylcarnitine), are observed. The disorder is caused by mutations in the *CPT1A* gene. The primary treatment corresponds to therapy for fatty acid beta-oxidation disorders. The global prevalence is less than 1 in 1,000,000.

Carnitine/palmitoyltransferase deficiency, type II (ICD-10 code — E71.3 Fatty acid metabolism disorder (carnitine/palmitoyltransferase deficiency, type II))

Elevated (C16+C18:1)/C2 ratios and decreased C0 (free carnitine) levels are observed. This condition is caused by mutations in the *CPT2* gene. Primary treatment corresponds to therapy for Type I. Carnitine is prescribed when free carnitine levels are low until C0 normalizes. The global prevalence is 1–9 per 100,000.

Carnitine/acylcarnitine translocase deficiency (ICD-10 code — E71.3 Fatty acid metabolism disorder (carnitine/acylcarnitine translocase deficiency))

The disorder is characterized by elevated (C16+C18:1)/C2 ratios and decreased C0 (free carnitine) levels, and caused by mutations in the *SLC25A20* gene. Primary therapy involves avoiding fasting (see above), a low-fat diet (30% fat in the diet: 20% medium-chain fatty acids with low caprylic acid (C10) content, 10% long-chain fatty acids), and administration of carnitine when free carnitine levels are low until C0 normalizes, followed by discontinuation. The estimated global prevalence is 1:1,000,000.

Glutaric acidemia, type II (ICD-10 code — E71.3 Fatty acid metabolism disorder (glutaric acidemia, type II (multiple acyl-CoA dehydrogenase deficiency); glutaric acidemia, type II (riboflavin-sensitive form))

Elevated concentrations of C4 (isobutyrylcarnitine), C5 (isovalerylcarnitine), C5-DC (glutaric acid carnitine), C6 (hexanoylcarnitine), C8 (octanoic acid-carnitine), C10 (decanoic acid-carnitine), C12 (dodecanoic acid-carnitine), C14:1 (tetradecenoic acid-carnitine), C16 (hexadecanoic acid-carnitine), C18:1 (octadecenoic acid-carnitine) are observed. The disorder is caused by mutations in the *ETFA, ETFB*, and *ETFDH* genes. Elevated levels of these metabolites are also observed in other riboflavin metabolism disorders and in cases of maternal riboflavin deficiency. Elevated levels of the following organic acids are detected in urine: glutamic acid, 2-hydroxyglutamic acid, isovaleric acid, 2-methylbutyrate, isobutyrate, isovalerylglycine, isobutyrylglycine, and others. The main treatment consists of a low-protein, low-fat diet, administration of riboflavin and carnitine, and management of metabolic crises. The global incidence is 1:300,000. The incidence of the disease in the Russian Federation, according to the Russian National Registry (RNS), is 1:205,233 live births [22].

Proximal spinal muscular atrophy 5q

(ICD-10 code — G12.0 Infantile spinal muscular atrophy, type I (Werding–Hoffmann); G12.1 Other hereditary spinal muscular atrophies)

This is an autosomal recessive disorder. Mutations in the *SMN1* gene lead to a reduction in SMN protein levels, resulting in damage to the spinal cord's α-motor neurons. Clinically, it manifests as progressive muscle atrophy, muscle weakness, and hypotonia. Based on clinical course and age of onset, four types of spinal muscular atrophy (SMA) are distinguished. During newborn screening using molecular genetic methods, a common mutation (95–98% of cases) in the *SMN1* gene is identified, that is a homozygous deletion of exon 7. Upon detection of a homozygous deletion, verification is performed at a reference center, and

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the number of copies of the *SMN2* gene, a gene 99% structurally similar to *SMN1*, is determined. As the number of *SMN2* gene copies increases, the severity of SMA's clinical presentation decreases. The number of *SMN2* copies determines the choice of targeted therapy. Etiopathogenic treatment has been developed to prevent the development of severe symptoms. Patients with SMA are monitored and treated by neurologists. In the presence of a clinical picture of SMA and the absence of pathology based on screening results, sequencing of the *SMN1* gene is required to rule out point mutations in this gene. The prevalence of the disease in the Russian Federation, based on the results of expanded neonatal screening for 2023–2024, is 1:8,439 [20].

Primary immunodeficiencies

(ICD-10 code — D80 Immunodeficiencies with predominant antibody deficiency; D81 Combined immunodeficiencies; D82 Immunodeficiencies associated with other significant defects; D83 Common variable immunodeficiency; D84 Other immunodeficiencies)

Congenital immune disorders are a diverse group of genetically determined diseases characterized by defects in components of the immune system. Primary immunodeficiencies are caused by genomic, chromosomal, and gene mutations. Screening for primary immunodeficiencies is performed using a molecular genetic method. Extrachromosomal circular structures formed during the differentiation of T-cell (TREC — T-receptor excision circle) and B-cell (KREC — kappa-deletion recombination excision circle) lymphocyte receptors are identified. The number of TREC/KREC copies reflects how many T and B cells have left the thymus and bone marrow and entered the bloodstream. A decrease in TREC/KREC levels below the threshold indicates a possible defect in the T- and B-cell components of immunodeficiency. Retesting and confirmatory diagnosis are performed using lymphocyte immunophenotyping by flow cytometry, as well as molecular cytogenetic and molecular genetic testing methods. The most common conditions identified by neonatal screening results are: severe combined immunodeficiency, Di George syndrome, Nijmegen syndrome, and agammaglobulinemia with B-cell deficiency. Patients are monitored by an immunologist. It should be noted that TREC/KREC screening does not detect all forms of primary immunodeficiencies [21].

CONCLUSION

Neonatal screening allows for early detection of the targeted diseases and the initiation of timely treatment. It is important to remember that despite normal levels of tested markers, a newborn should be re-examined and/or referred for consultation with an appropriate specialist if there is clinical suspicion of a disease that can be diagnosed through neonatal screening. Identifying a hereditary disease in a family makes it possible to provide medical-genetic counseling and assist parents in having a healthy child, including the use of assisted reproductive technologies.

ADDITIONAL INFORMATION

Author contribution. D.O. Ivanov — significant contribution to the concept and design of the article, data collection and analysis; L.V. Lyazina — collection of information on nosological forms of diseases included in the diagnosis of neonatal screening, data on the frequency of occurrence, description of the clinical picture, and preparation of the article; L.A. Fedorova — collection of data and description of the clinical picture in the neonatal period for nosological forms, and final approval.

All authors read and approved the final version before publication.

Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Д.О. Иванов — существенный вклад в замысел и дизайн статьи, сбор и анализ данных; Л.В. Лязина — сбор информации по нозологическим формам заболеваний, входящих в диагностику неонатального скрининга, данные по частоте встречаемости, описание клинической картины, подготовка статьи; Л.А. Федорова — сбор данных и описание клинической картины в неонатальном периоде для нозологических форм, окончательное одобрение статьи.

Все авторы прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

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ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)