Mini Review

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Looking for a needle in a haystack: a case study of rare disease care in neonatology

https://doi.org/10.1515/jpm-2025-0090
Received February 18, 2025; accepted March 30, 2025;
published online April 17, 2025

Abstract

Objectives: Rare diseases (RDs) collectively affect approximately 400 million individuals globally, including newborns and children. These conditions often involve genetic, metabolic, or congenital disorders and are challenging to diagnose and manage due to their subtle or non-specific symptoms. Aim is to emphasize the need for specialized, multidisciplinary, and technology-driven approaches to improve outcomes for neonates with RD.

Methods: A comprehensive review of the infrastructure, diagnostic approaches, and clinical care strategies for RDs in neonates was conducted. The Department of Neonatology and Rare Diseases at the Medical University of Warsaw was analyzed as a model for centralized care, integrating prenatal consultations, advanced diagnostics, and multidisciplinary treatment.

Results: The department offers specialized care for neonates with RDs, including intensive care, advanced diagnostic tools, and personalized therapies such as pharmacological interventions and surgery. Collaboration with a perinatology center ensures prenatal consultations, delivery planning, and early interventions, while the proximity of operating rooms to neonatal units enhances outcomes. Genetic counseling plays a pivotal role in supporting families and expanding newborn screening programs with emerging osmic technologies which can significantly improve early diagnosis and management.

Conclusions: Centralized, multidisciplinary care and advancements in diagnostic technologies are essential for improving outcomes for neonates with RD. The integration of clinical care, genetic counseling, and innovative screening programs highlights the importance of specialized centers in addressing the unique challenges of these conditions.

Keywords: rare diseases; neonatology; newborn screening; genetic counseling; congenital disorders

Introduction

RDs are uncommon individually, but collectively they affect a significant number of people worldwide. Currently, between 6,000 and 8,000 RDs have been identified, with new conditions emerging in published investigations. While individual RDs are uncommon, together they impact around 400 million people globally [1]. Around one in 16 people worldwide live with some form of RD, including many newborns and children.

Typically severe, chronic, and progressive, RDs extend their impact beyond the diagnosed individual to families, healthcare systems, and society [2]. A significant proportion of RDs are genetic in origin. They can affect various organs and manifest as multi-defect syndromes, isolated developmental abnormalities, or conditions impacting intellectual development, as well as the neurological, cardiac, renal, endocrine, gastrointestinal, dermatological, ophthalmological, or immunological. Some may also involve oncological and infectious diseases. Consequently, almost every medical professional is likely to encounter a patient with a RD during their career.

The clinical manifestations of RDs are highly variable, with symptoms differing not only between diseases but also among individuals with the same condition. For many rare diseases, early signs may appear during the neonatal period or even be detected through prenatal screening or diagnostic testing. Pediatricians and neonatologists must stay vigilant, as over 50 % – and possibly up to 70 % – of rare diseases affect children [3–10]. Many of these conditions present symptoms at birth or during the neonatal period, making

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Table 1: Different definitions of rare and ultra-rare diseases based on their incidence [5–11].

Region/organization	Definition – incidence
World Health Organization (WHO)	<65/100,000
Rare disease international	<50/100,000
United States of America (USA)	Less than 200,000 people in the country, <86/100,000
European Union (EU)	<50/100,000
Asia	<40/100,000
Australia	<11/100,000
Sweden	<10/100,000
England – ultra-rare disease	<2/100,000
Poland – ultra-rare disease	Less than 750 in population, <2/100,000

early diagnosis essential. However, diagnosing rare diseases in newborns is particularly challenging, as their symptoms often resemble those of more common neonatal conditions, leading to frequent misdiagnoses [2, 3, 6, 10]. A single, universal definition of RDs does not exist globally. The World Health Organization (WHO) defines a RD as a life-threatening or chronic condition affecting fewer than 65 per 100,000 people [7–9]. However, definitions vary by region, with approximately 296 different definitions from 1,109 organizations [10]. Different criteria for the definition of rare disease are shown in Table 1 [5–11].

Ultra-rare diseases are an even smaller subset, affecting only 1 in 100,000 people, 1 in 1,000,000, or, in some cases, just a handful of individuals worldwide [6]. Additionally, some diseases are rare within certain populations but not in others. For instance, Tay–Sachs disease is rare in the general population but has a carrier frequency of 1 in 25 among Ashkenazi Jews [4]. Tuberculosis is rare in the United States but remains one of the top 10 causes of death globally, as reported by the WHO [3]. Similarly, thalassemia is uncommon in Northern Europe but prevalent in the Mediterranean region, and “periodic disease” is rare in France but common in Armenia. Furthermore, certain common diseases may have rare variants [3–9].

RDs in newborns pose unique challenges for diagnosis and treatment. These diseases are often difficult to identify due to their rarity and the subtle or non-specific nature of early symptoms. RDs exhibit a wide spectrum of clinical manifestations and severity levels, making classification difficult in many cases [6]. Specialized databases, such as Orphaned, have been created to address these challenges [2]. Orphaned provides comprehensive information on RD prevalence, clinical features, and treatment guidelines [2]. It includes over 4,000 disorders and promotes consistency in terminology and data sharing across countries [2]. Rare disease diagnoses are typically coded using the International Classification of Diseases (ICD) and specialized ORPHA codes, facilitating global standardization and supporting statistical analysis [6].

Historical perspectives on neonatal care and rare diseases

Over the centuries, neonatal care has evolved from rudimentary practices to the highly specialized field of neonatal medicine. Historically, newborn care was rooted in cultural practices and traditional medicine. Historically, infant mortality rates were alarmingly high due to factors such as malnutrition, infections, and birth complications [12, 13]. In the early days of neonatal medicine, treatment options for premature infants and congenital abnormalities were limited and often ineffective.

Significant progress in medical science began in the 19th century, with notable advances such as the development of respiratory support and surfactant therapy, which improved the survival rates of premature and critically ill newborns [12]. The 20th century brought further advancements in neonatal care, resulting in a significant reduction in infant mortality rates [12, 13]. Progress in addressing common neonatal problems such as infections, respiratory and cardiac failure, and malnutrition played a pivotal role in this improvement [12].

The 21st century has ushered in new innovations in neonatal care, including the development of advanced technologies. Enhancements in neonatal transport systems in the 1970s in the United States of America (USA) and Canada have enabled the safe transfer of critically ill newborns to specialized centers, ensuring they receive the care they need without delay [12–15].

In the 1970s, public health programs in the USA and Canada introduced and formalized the concept of regionalized perinatal care [14]. This system stratified maternal and neonatal care into different levels of complexity, recommending the referral of high-risk patients to higher-level centers equipped with the necessary resources, as shown in Table 2 [15]. The goal was to organize healthcare services for high-risk newborns, ensuring that they were delivered in facilities with highly qualified and experienced medical personnel and access to the required equipment and technology for optimal and definitive care. Similar programs were subsequently implemented in developed European countries [14]. In Poland, the Perinatal Care Improvement Program has been in place since 1995 [14]. The increased availability of neonatal intensive care has markedly

improved outcomes for high-risk infants, including those born prematurely or with serious medical or surgical conditions [14, 15].

Efficient and safe neonatal transport systems are a crucial component of these programs. The preferred and safest method is *in utero* transport, which reduces the risks associated with the postnatal transfer of critically ill newborns [15]. High-risk pregnancies should be managed in facilities equipped to provide the necessary neonatal care immediately after birth, as mortality and post-treatment morbidity rates are significantly lower when definitive treatment is available at the place of birth, eliminating the need for postnatal transport [14, 15]. This approach ensures that newborns receive timely and appropriate treatment. When postnatal transfer becomes necessary, it should be conducted by experienced medical personnel who can maintain the infant's stability during transportation [14, 15].

Table 2: Regionalization of neonatal care based on pregnancy risk [15].

Level I	– Basic level of care for low-risk neonates – Provide neonatal resuscitation – Provide routine postnatal care – Care for physiologically stable preterm infants from 35 to 37 weeks' gestation. – Stabilization of sick preterm infants less than 35 weeks' gestation until transfer to a higher level of care
Level II	Level I capabilities plus: – Provide care for preterm infants born at ≥32 weeks of gestation and weighing ≥1,500 g who exhibit physiological immaturity or are moderately ill with conditions expected to resolve quickly and not requiring urgent subspecialty services. – Provide care for infants recovering from intensive care. – Offer mechanical ventilation for brief durations (<24 h), continuous positive airway pressure (CPAP), or both. – Stabilize infants born before 32 weeks' gestation or weighing less than 1,500 g until transfer to a higher level of care.
Level III NICU	Level II capabilities plus: – Provide sustained life support. – Offer comprehensive care for infants born at <32 weeks'gestation, weighing <1,500 g, and for infants of all gestational ages and birth weights with critical illnesses. – Ensure prompt and readily available access to a full range of pediatric medical subspecialists, pediatric surgical specialists, pediatric anesthesiologists, and pediatric ophthalmologists. – Provide a full spectrum of respiratory support, including conventional and/or high-frequency ventilation and inhaled nitric oxide. – Perform advanced imaging, with urgent interpretation, including computed tomography (CT), magnetic resonance imaging (MRI), and echocardiography.
Level IV Regional NICU	Level III capabilities plus: – Located within an institution capable of providing surgical repair for complex congenital or acquired conditions. – Maintain a comprehensive range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric anesthesiologists on-site. – Facilitate transport services and offer outreach education.

NICU, Neonatal Intensive Care Unit.

Regionalized systems of perinatal care are essential to ensuring that every newborn is delivered and cared for in a facility best suited to their healthcare needs. This system facilitates the achievement of optimal health outcomes and underscores the importance of proper coordination and resources within perinatal and neonatal care networks.

Global initiatives aimed at enhancing maternal and child health are transforming healthcare systems worldwide. The main goal is increasing access to maternal health services in low-income countries by organization of specialized centers, which include neonatal units. These centers provide specialized care for newborns, particularly those born prematurely or with critical conditions, ensuring optimal outcomes. Organizations committed to improving maternal and infant health play a vital role in this transformation. They focus on developing clinical guidelines for maternity hospitals and advancing perinatal medicine. These guidelines help standardize care, promote best practices, and ensure mothers and their children receive the highest quality healthcare. By combining infrastructure development with evidence-based practices, these initiatives contribute significantly to reducing maternal and neonatal mortality [14, 15].

Rare diseases: current status and challenges

Maternal and perinatal morbidity and mortality are very sensitive indicators of the strengthening of the healthcare system reflecting the quality of maternal and neonatal care as well as broader socio-economic conditions [16]. Over the past 50 years, significant progress has been made in reducing neonatal mortality rates in developed regions such as Europe and the USA. Mortality has declined from 1.5 % to 0.2–0.3 %, thanks to advances in science and healthcare systems [13]. This remarkable improvement is primarily attributed to the effective management of conditions such as infections, asphyxia, respiratory distress syndrome, hemolytic disease, and birth injuries [12, 13]. Despite these achievements, congenital anomalies remain a significant challenge in neonatal care [17–19].

Currently, congenital anomalies are the second leading cause of neonatal mortality globally, following complications related to prematurity [17–19]. In Europe, they account for 25–27 % of neonatal deaths [19]. In Poland, congenital anomalies are responsible for approximately 32 % of neonatal mortality [18]. Furthermore, congenital anomalies are the leading cause of death in children under five, both in Europe and in Poland [18–20]. Improving outcomes requires timely and accurate diagnosis to facilitate the introduction of appropriate treatment. However, diagnosing congenital anomalies can be challenging, particularly when symptoms are subtle or overlap with other conditions [3]. Advanced diagnostic tools, such as imaging techniques and genetic testing, are essential in overcoming this challenge [21]. The growing emphasis on genetics in neonatal diseases has significantly improved diagnostic accuracy, paving the way for targeted interventions and personalized care strategies [21–25].

While significant progress has been made, there is still room for improvement in reducing infant mortality caused by congenital anomalies [26]. Achieving better neonatal outcomes emphasizes the need for sustained investment in research, technology, and education for both healthcare providers and the public [22, 27].

Newborn screening forms the foundation of modern healthcare, offering the potential to prevent severe diseases and promote better health outcomes [22, 28]. While considerable progress has been achieved in high-income countries, there remains an urgent need to expand these programs globally, particularly in low- and middle-income countries, where disparities in access to healthcare pose a major challenge [9]. Ensuring that all infants, regardless of their geographical location or socio-economic status, have access to early diagnosis and treatment can significantly reduce the burden of RDs and improve the health and well-being of future generations [2, 5, 29].

Healthcare providers should be trained to recognize the signs and symptoms of RD. Advances in genetic testing and specialized care have the potential to significantly improve early diagnosis and treatment outcomes [2, 5, 29, 30].

In low- and middle-income countries, treatments for RDs are often unavailable. This is due to factors such as limited financial support for therapies, complex regulatory requirements for drug approval, lack of reimbursement mechanisms, inadequate administrative infrastructure, and low awareness of diagnostic and treatment options. The International Rare Diseases Research Consortium has established the Rare Disease Treatment Access Working Group with the primary goal of developing an essential list of medicinal products for rare diseases [31]. These medications are classified into seven disease groups – metabolic, neurological, hematological, anti-inflammatory, endocrine, pulmonary, and immunological – along with a miscellaneous category [31].

Orphan drugs are pharmaceuticals specifically developed to treat RDs, addressing the unmet medical needs of affected patients [31]. Developing orphan drugs presents unique challenges, including complexities in designing clinical trials, defining meaningful outcomes, recruiting representative patient populations, addressing ethical concerns, and managing the high costs associated with therapies for small patient groups [31]. Moreover, the probability of success and predictability are often lower compared to treatments for more prevalent conditions, making this a high-risk area for investment [31].

To overcome these obstacles, a collaborative approach is essential. Effective partnerships between academic institutions, pharmaceutical companies (both small and large), patient advocacy groups, and health authorities are critical [31]. The ultimate objective of orphan drug development is to provide patients with RDs access to therapies that offer a favorable benefit-risk ratio [31]. By bridging gaps in treatment availability and ensuring that therapeutic innovations are both effective and accessible, the field of orphan drugs continues to play a pivotal role in transforming the lives of individuals with RDs [32].

Case study: Department of Neonatology and Rare Diseases at Warsaw Medical University

In recent years, the European Union (EU) has taken significant steps to designate centers with expertise in the medical care of patients with RDs [2]. Similar initiatives have been implemented in Poland, where specialized units focus on the diagnosis and treatment of specific groups of RDs [33].

The Department of Neonatology and Rare Diseases (DNRD) at the Medical University of Warsaw (MUW) has been established to provide comprehensive care for newborns, including those with rare diseases. The majority of rare diseases presented in newborn period are inborn errors of metabolism, genetic syndromes and congenital anomalies. Severe, surgically correctable, and potentially life-threatening congenital anomalies or unusual symptoms requiring extensive diagnostics and treatment. The department caters to critically ill neonates requiring intensive care, as well as those in stable condition who need diagnostic evaluation. Located within the Clinical Children's Hospital (CCH), the department benefits from access to a wide range of professional diagnostic procedures and consultations

with specialists. Additionally, the Department of Obstetrics and Perinatology (DOP), which includes a delivery room, is situated in the same facility. This proximity allows for the immediate transfer of neonates to the Newborn Intensive Care Unit (NICU) if required. High-risk pregnancies receive thorough prenatal diagnostics and, when necessary, specialized perinatal procedures, ensuring optimal planning for delivery and postnatal management.

Neonatologists work closely with perinatologists and other relevant specialists, such as surgeons, cardiologists, neurosurgeons, anesthesiologists, and radiologists, to provide multidisciplinary care. Many patients present with congenital anomalies, such as congenital diaphragmatic hernia, omphalocele, gastroschisis, spina bifida, anal atresia, esophageal atresia or large tumors, which may necessitate surgical intervention within the first hours or days of life. For such cases, postnatal surgical or procedural interventions are planned in advance. Each year, the DNRD treats approximately 2,200 patients, including referrals from across the country.

Special group are patients with congenital diaphragmatic hernia, numbering around 30–40 annually, require meticulous planning from delivery through surgery, which is often performed between the third and fifth day of life when the patient is stable. Surgical procedures are conducted in an operating room within the same building to minimize risks associated with transporting critically ill newborns. When a patient's condition is critical, surgery may be performed in the neonatology department to prevent destabilization during the transfer of the critically ill newborn.

Another complex group includes neonates with congenital heart defects (CHD), who may be either stable or critically ill. These patients require precise prenatal diagnostics and consultations with cardiologists and cardiac surgeons to plan treatment. In cases where urgent procedures, such as balloon atrial septostomy, are needed, prompt echocardiographic evaluation and Angio tomography may be performed to guide therapy.

Neonates with large tumors, such as teratomas or hemangiomas, present significant challenges as well. These patients are prenatally evaluated by surgeons and interventional radiologists. Postnatal diagnostics often include advanced imaging, such as computed tomography or magnetic resonance imaging, to plan surgical or interventional procedures.

Neonates requiring neurosurgical interventions, such as those with spina bifida, encephalocele, or hydrocephalus, also benefit from multidisciplinary care. Collaboration with neurosurgeons ensures proper diagnostics and treatment, with pre- and postoperative care provided in the neonatology department to ensure continuity of care. For spina bifida patients, urological issues, such as neurogenic bladder, are addressed with consultations and thorough diagnostic procedures before discharge.

Neurological and metabolic disorders frequently manifest after birth or are identified through newborn screening. Many such patients are referred from other hospitals and require comprehensive diagnostics, including genetic testing and imaging, as well as individualized treatment plans and consultations with neurologists and geneticists.

Premature and low birth weight neonates with congenital defects form a particularly vulnerable group. These patients face challenges related to immaturity and the associated complications of their defects. Planning surgeries, especially cardiac procedures, is particularly complex in such cases. Many neonates with ductal-dependent congenital heart disease require continuous prostaglandin infusions for weeks until they achieve an appropriate weight for cardiac surgery.

Neonates with multiple congenital anomalies require carefully coordinated diagnostic and therapeutic processes to achieve the best possible outcomes.

Patients who require it receive care from physiotherapists and speech therapists to support their development. Family-centered care is a priority, recognizing the vital role of parental presence in the therapeutic and discharge process. For families traveling from distant regions, accommodations are provided to support their stay and active involvement in their child's care during hospitalization.

Newborn screening for rare diseases

Newborn screening (NBS) is a practice aimed at identifying potentially severe illnesses before the onset of symptoms, with the goal of reducing mortality and morbidity through early intervention. By detecting RDs PR symptomatically, NBS can significantly improve health outcomes through timely diagnosis and appropriate treatment, often preventing severe developmental or physical impairments [30].

NBS has been introduced by Robert Guthrie in the early 1960s for phenylketonuria using blood samples collected on filter paper, a relatively simple and effective method [22]. Over the subsequent decades, the number of conditions included in NBS programs gradually expanded. Major progress occurred in the late 1990s with the introduction of tandem mass spectrometry (MS/MS), which enabled the simultaneous screening of numerous metabolic disorders using a single blood spot [34]. This advancement increased

the number of detectable conditions to 40 to 50 diseases [28]. The advent of molecular technologies, such as polymerase chain reaction (PCR), has further enhanced NBS by facilitating the screening of additional conditions, including cystic fibrosis, severe combined immunodeficiency (SCID), and spinal muscular atrophy (SMA) [22]. These technological advancements have made NBS programs more comprehensive, allowing for the detection of an increasing number of disorders [22–24, 28].

Currently, NBS is available in many countries worldwide, although its adoption and the range of screened diseases vary depending on prevalence, healthcare systems, resources, and national priorities [28]. While NBS is well-established in many high-income countries as part of national public health initiatives, its availability remains limited in low- and middle-income countries [9]. In developed nations, NBS programs are typically efficient and well-organized, whereas in low-income countries, they are often unavailable. Even in middle-income countries, where NBS is relatively new, programs may be underdeveloped or poorly coordinated [9]. Disparities in standardized programs, financial limitations, and restricted access to modern diagnostic technologies contribute to these challenges [2, 5, 6, 28].

NBS usually comprises two main components: point-of-care testing and dried blood spot (DBS) testing. Point-of-care screening tests are conducted in neonatal units and typically include hearing screening and screening for critical congenital heart diseases (CCHD). Despite routine antenatal ultrasounds and postnatal physical examinations, up to one-third of infants with CCHD may be discharged before a diagnosis is made. Pulse oximetry testing, a non-invasive, reliable, and straightforward method, offers high sensitivity and specificity for early detection of CCHD [35, 36].

Similarly, early hearing screening provides opportunities for timely intervention, significantly improving language, speech, and communication skills [30]. Early diagnosis of hearing impairment and early intervention in affected infants are crucial for prevention of long-term developmental delays [25, 28, 30].

Current NBS programs vary globally in the number of conditions included and general screening practices. In Europe, for instance, 85–100 % of newborns undergo some form of screening, with programs covering between 2 and over 40 disorders [25]. In the USA, nearly 100 % of newborns are screened, with programs encompassing 35 core conditions and 26 secondary conditions [23].

In the European Union (EU), differences in NBS programs persist among member states. The Council of the EU and the former Committee of Experts on Rare Diseases have recommended coordinated action at the EU level while respecting the autonomy of individual nations to tailor programs to their specific needs [28]. However, challenges remain in ensuring effective and comprehensive NBS implementation across all countries, regardless of their resources [28].

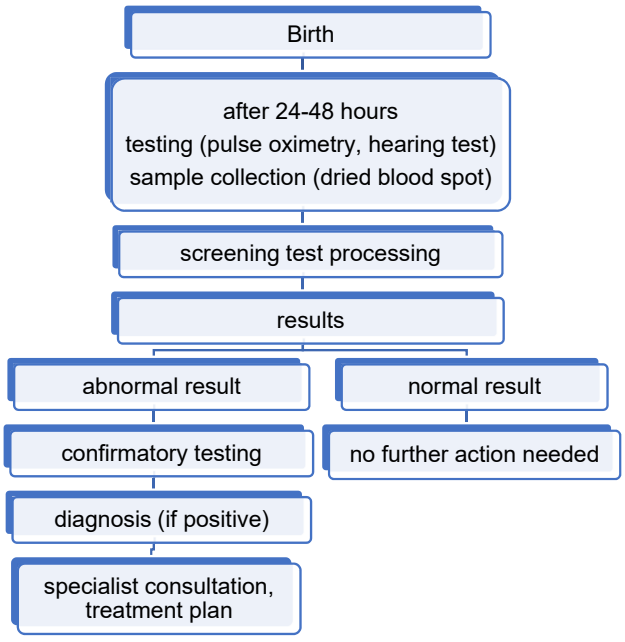

Figure 1: Flowchart of newborn screening in Poland [37, 38].

In Poland, newborn screening has evolved significantly since 1994, starting with tests for phenylketonuria and congenital hypothyroidism [37, 38]. Pilot tests for cystic fibrosis began in 1999, gradually covering the entire population [37, 38]. In 2000, the first mass spectrometer was installed at the Screening Department to detect congenital metabolic defects, and pilot mass spectrometry screening tests were officially launched in 2002 [37, 38]. By 2014, all newborns were included in NBS [37, 38]. Screening for congenital adrenal hyperplasia (CAH) began in 2015, followed by tests for biotinide deficiency in 2016–2017 [37, 38]. In 2018, additional testing for the risk of developing type 1 diabetes was introduced [37, 38]. By 2021, screening programs had expanded to detect SCID, galactosemia, familial hypercholesterolemia, and SMA [37, 38]. Currently, newborn screening in Poland includes 29 genetic diseases [37, 38]. Flowchart of newborn screening in Poland is shown in the Figure 1 [37, 38].

Future directions in the management of rare neonatal diseases

NBS is one of the most successful public health initiatives. Early diagnosis and treatment are available for many

conditions; however, its efficacy is significantly reduced if initiation is delayed beyond the first few months of life [21]. Identifying life-threatening conditions during the newborn period enables timely intervention and improved outcomes [22, 28, 30]. Traditional NBS using tandem mass spectrometry (MS/MS) has allowed screening programs to test effectively for dozens of conditions at a low cost [22, 24]. However, it is limited to detecting blood- or urine-based metabolic biomarkers [21–25, 34]. Many genetic conditions without metabolic biomarkers remain systematically unscreened [39].

The rapid development of genomic sequencing technologies, including next-generation DNA sequencing (NGS), has revolutionized the diagnosis of RDs [21, 22]. These technologies have expanded the scope of screening to include disorders without easily detectable biochemical biomarkers [25, 32]. Genomic sequencing has significantly improved diagnostic accuracy and is now an invaluable tool for diagnosis of many RDs [40]. Across Europe, numerous initiatives are being developed to explore the utility and feasibility of incorporating NGS into NBS programs [34].

The future of NBS lies in a multi-omics approach that combines genomics, metabolomics, and other molecular techniques [22]. Genomic newborn screening involves analyzing DNA to detect a broader range of genetic disorders [22]. Further advancements in genomic technologies and increased access to these tools could accelerate the diagnosis of RDs and enable more personalized and effective treatments [27, 34]. However, the widespread adoption of genomic screening faces challenges, including high costs, ethical considerations and public acceptability concerns [27]. Metabolomics, which involves analyzing metabolic profiles, offers the potential to deepen insight into disease phenotypes and identify both known and novel biomarkers for RDs [22, 32, 34].

Advancements in bioinformatics and the development of patient data registries have also contributed to breakthroughs in gene identification and nucleic acid-based therapies [34]. These advancements have paved the way for gene therapy and molecular treatments, offering new hope for patients with RDs [39–41].

Conclusions

In conclusion, while RDs in newborns present significant challenges, specialized centers such as the Department of Neonatology and Rare Diseases at Warsaw Medical University play a crucial role in their diagnosis and treatment. Early detection, personalized care, and ongoing research are essential for effectively managing these conditions and improving patients' quality of life.

The work carried out at the Department of Neonatology and Rare Diseases at Warsaw Medical University exemplifies the intricate and meticulous process of identifying and treating rare diseases in neonates. Much like searching for a needle in a haystack, the quest to diagnose these conditions requires precision, expertise, and dedication. Through advanced diagnostic techniques, interdisciplinary collaboration, and commitment to research, this institution continues to shed light on rare neonatal disorders, offering hope to affected infants and their families.

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: The authors state no conflict of interest.
Research funding: None declared.
Data availability: Not applicable.

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