

NEWBORN SCREENING, DIAGNOSIS, AND MANAGEMENT OF INHERITED METABOLIC DISORDERS: STATUS AND PROGRESS OF THE SOUTHERN MEDITERRANEAN COUNTRIES

E. PORCÙ¹, E. POSTOLI², P. CULLUFI³, L. SANTORO⁴, D. CRISCI⁵, C. S. SIDIRA⁶,
P. AUGOUSTIDES-SAVVOPOULOU^{7,8}, A. SKOUMA⁹, O. GRAFAKOU¹⁰

• • •

¹Division of Inherited Metabolic Diseases, Department of Women's and Children's Health, University Hospital of Padua, Padua, Italy

²Neonatology Division, Hygeia International Hospital, Tirana, Albania

³Pediatrics Department, University Hospital "Mother Teresa", Tirana, Albania

⁴Pediatrics Clinic, Ospedali Riuniti, Presidio Salesi, Ancona, Italy

⁵CEINGE Biotecnologie Avanzate, Naples, Italy

⁶Consultant in Paediatric Metabolic Medicine, Thessaloniki, Greece

⁷Medical Faculty, Aristotle University of Thessaloniki, Thessaloniki, Greece

⁸KRIKOS ZOIS Greek Patient Society for Inherited Metabolic Diseases, Thessaloniki, Greece

⁹Department of Newborn Screening, Institute of Child Health – Medical Division, Athens, Greece

¹⁰Department of Pediatrics, IEM Clinic, Archbishop Makarios III Hospital, SHSO Services, Nicosia, Cyprus

CORRESPONDING AUTHOR

Elena Porcù, MD; elena.porcu@aopd.veneto.it

ABSTRACT – Objective: Efficient management of inherited metabolic disorders requires early diagnosis through newborn screening, confirmatory diagnostic analyses, follow-up of detected patients, and availability of therapeutic resources. The aim of this work is to share the present state of newborn screening (NBS) programs in Mediterranean countries and discuss urgent needs and possible actions.

Materials and Methods: A group of experts from Albania, Cyprus, Greece, and Italy met to discuss the disparities among countries regarding practices, regulations, resources, and expertise necessary to manage inherited metabolic disorders. As Italy has a long experience with newborn screening, the Italian participants acted as moderators of the meeting and suggested possible actions to address the problems in the Mediterranean region.

Results: Differences and disparities among countries regarding practices, regulations, resources, and expertise in the management of inherited metabolic disorders emerged.

Conclusions: All participants call for collaboration among countries to promote efforts for cultural advancements, economic resource gathering, and regulatory changes in Mediterranean countries.

KEYWORDS: Newborn screening, Mediterranean area, Inherited metabolic disorders, Albania, Cyprus, Greece.

INTRODUCTION

Newborn screening (NBS) is a complex, integrated, multidisciplinary secondary health prevention program that aims to identify diseases before symptoms are detected. Thus, it enables early initiation of medical care to prevent adverse outcomes¹.

Across Europe, there are vast discrepancies in the number of screened diseases and the regulation of NBS. More than 25 diseases are on the screening panel in some countries, such as Italy, Portugal, Austria, and Greece fewer than 10 diseases in the UK and France, and only two in Romania and Cyprus. Of note, Albania and part of Kosovo do not follow official NBS programs yet. Some local initiatives are carried out under the responsibility of autonomous parts of the countries²⁻⁴.

The introduction of innovative high-throughput technology, such as tandem mass spectrometry, in many clinical laboratories across Europe, has led to the gradual enlargement of the panel of screened conditions. The expanded NBS panel generally includes aminoacidopathies, urea cycle disorders, organic acidurias, and fatty acid beta-oxidation deficiencies⁵.

Recent efforts by scientists and authorities aim to accelerate the expansion of evidence-based screening programs and minimize disparities in Europe^{3,6}. For instance, an NBS program was initiated in Greece in 1974, sponsored by the Ministry of Health and Welfare, and administered by the Institute of Child Health. This program includes the screening for phenylketonuria (PKU), congenital hypothyroidism (CHT), galactosemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency, with confirmatory analysis as an integral component⁷.

Other southern European countries have minimal or absent screening programs. Common obstacles to NBS implementation include limited economic resources, inadequate health education, insufficient government support, and a substantial number of out-of-hospital births².

A panel of experts from Albania, Greece, and Cyprus met to share the present state of NBS programs in their countries and discuss urgent needs and possible actions. Italian experts were present to moderate the meeting and to compare the long history and experience in NBS in Italy with the situation in other countries. This article presents the information shared at the board meeting and the suggestions that emerged from the discussion.

MATERIALS AND METHODS

Expert pediatricians and laboratory professionals from Greece, Cyprus, Albania, and Italy, involved in national NBS programs and/or in managing subjects with inherited metabolic disorders (IMDs) and considered knowledgeable on key aspects, met in a virtual meeting on 31 January 2024.

In preparation of the meeting, all participants from Greece, Cyprus, and Albania responded to a questionnaire ([Supplementary material](#)), distributed by e-mail, on the situation of NBS and IMD management in their respective countries in 2023. The topics discussed covered the main aspects of NBS, including the diagnostic pathway for IMDs in each country's clinical practice and management principles, problems, and resources. The results of the questionnaire were presented during the meeting and here reported, together with the further information about IMDs management that were collected and discussed by the participants. Italian experts reported their experience during the discussion as a basis for suggesting actions. Although NBS programs in some countries include screening for conditions other than IMDs, this article focuses on NBS for IMDs.

RESULTS

NBS: Organization and Perspectives

The birth rate in Albania has significantly decreased since 1990 due to political changes and is today around 25,000–30,000 newborns/year. Most inhabitants live in the Tirana district, and most births occur in this area.

There is no national NBS program in Albania. Screening is only performed voluntarily in non-public hospitals within paid birthing services; dried blood spots are collected from newborns and sent to a foreign laboratory for analysis. These paid services only succeed in catching around 7% of the total births, thus screening is performed in a minority of the Albanian population.

In Cyprus, NBS started in 1988 and, at present includes only PKU and CHT. Screening only for selected diseases reflects a conservative strategy. Recommendations from a specialists committee to include eight IMDs were put forward in 2016 and a formal decision to expand was made in 2022; however, the program is still unmodified for several reasons including doubts about the availability of therapeutic opportunities. Nevertheless, empirical data suggest expanding screening to a broader spectrum of diseases. Experts and local health authorities are currently considering expanding NBS program by introducing tandem mass spectrometry. Operational aspects of NBS in Cyprus present unique challenges, particularly the division of laboratory testing into two separate facilities. This dual testing location requires a well-coordinated strategy to efficiently manage and transport samples. The geographic compactness of Cyprus offers a logistical advantage, mitigating potential complexities arising from this dual-laboratory approach. Collaborative efforts in NBS and the broader field of genetic disorders in Cyprus have been informal so far, often relying on personal networks and regional partnerships, particularly with Greece and Israel. Formal national-level collaborations could potentially enhance the effectiveness and scope of NBS services.

In Greece, a tandem mass spectrometer was introduced 2 years ago, overcoming previous financial constraints and resulting in recent advances in NBS efficiency. This acquisition paves the way for expanding the NBS program in 2024, with a strong emphasis on domestic and international collaboration. Greek biochemists have sought expertise from Austria, among other countries, to improve their knowledge of NBS and IMD management. Despite some technical challenges, there is optimism about the possibility of overcoming these hurdles and initiating the expanded screening program in 2024 beyond PKU and galactosemia to include other IMDs, particularly those at acute decompensation risk. The information reported by participants is reported in Table 1.

Table 1. Demographic data and resources for NBS (population data from the United Nations Organization).

	Population (million)	Births/year (n)	Public NBS programs	Number of diseases screened	Tandem mass spectrometry availability	Private NBS practices	Plan for further NBS expansion
Albania	2,750,000	28,000–30,000	No	0	No	Yes	No
Cyprus	1,700,000	10,000	Yes	2*	Yes	Yes	Yes, on the way
Greece	10,500,000	73,000	Yes	29**	Yes	Yes	Yes

*Congenital hypothyroidism and phenylketonuria,

**Among these: G6PD deficiency, congenital hypothyroidism, phenylketonuria, galactosemia and cystic fibrosis.

The diagnosis of IMDs

The lack of a national NBS program in Albania is associated with a delay in the diagnosis of all IMDs and some undiagnosed patients, resulting in poor outcomes.

One center for the diagnosis and management of cystic fibrosis (CF) treats and follows up about 150 children. Another operates to follow up on other rare metabolic disorders, and the Gaucher Unit is the best-structured one.

Between 2017 and 2021, through collaboration with a very specialized laboratory in Germany, all individuals who presented with symptoms suggestive of a genetic disorder could be tested for rare diseases (Case Finding Study). More than 5,000 genetic tests were performed, and in many cases, all family members were screened. In most cases, whole exome sequencing (4/5) was performed, while others underwent whole genome sequencing testing. The results were very impressive: about 1,000 patients with inborn errors of metabolism or neurodegenerative disorders were diagnosed.

These data show the emerging need to implement a national NBS program in Albania.

The infrastructure for diagnosing metabolic conditions in Cyprus is robust, anchored by the Biochemical Genetics Department of the Institute of Neurology and Genetics. This center stands out for its comprehensive metabolic and genetic testing services, and supports clinicians, mainly in Archbishop Makarios III Hospital, the tertiary hospital for Mother and Child in Cyprus, equipped to manage complex

cases. Other laboratories also offer genetic investigations, performed locally. This setup is essential for advancing the care for inborn errors of metabolism, which, despite being traditionally overseen by geneticists, has lately received more specialized focus. This shift aims to ensure that these conditions are not only accurately diagnosed but also effectively treated and managed in the long term.

In Greece, accessibility to genetic testing for the diagnosis of IMDs is not standardized nationwide. Patients or their families have to bear the financial burden of these expensive tests, as national healthcare reimbursement programs do not cover them. Consequently, individuals with financial means may opt for genetic testing to confirm diagnoses. In contrast, those facing financial constraints rely on more affordable biochemical tests, such as blood amino acids and organic acids analyses, for diagnostic purposes.

Management of IMDs (Treatment and Follow-Up)

In Albania, a center operates and follow up rare metabolic disorders, particularly pediatric and adult patients with Gaucher disease, where enzyme replacement therapy is available.

An important aspect is that health insurance funds do not fully cover the treatment of rare diseases, and most patients migrate to other countries for treatment and follow-up. Adults with IMDs are generally followed up by adult services.

In Cyprus, it was common practice to send patients abroad for the treatment of acute inborn errors of metabolism, specifically to countries such as Israel, Greece, or the UK. In recent years, this trend has changed, and efforts have focused on strengthening domestic capabilities to manage such emergencies.

In cases where medical interventions cannot be provided within Cyprus, applications are submitted for special permits to send patients abroad. However, there is currently no collaboration with a specialized metabolic center, as no patients have been sent abroad in recent years.

Another significant hurdle in this endeavor has been the healthcare system's policy on pharmaceutical procurement, which has restricted the pre-purchase of emergency medications. This policy poses challenges in ensuring the immediate availability of critical treatments. Efforts are underway to reform this policy, and now emergency medication stockpiling is possible, thus improving the response to acute metabolic crises in the country.

In Greece, medication for metabolic disorders is provided at a national level. Dietary management is problematic in some areas in the northern Greece as due to lack of metabolic dietitians. The aim is to collaborate across regions and with neighboring countries, including Cyprus, to establish a national registry for IMDs. This registry would encompass aspects of NBS and case management and facilitate care coordination for metabolic patients.

Regarding acute medication administration in Greece, considerable obstacles were encountered in securing essential drugs for emergency management. These challenges stemmed from prohibitive costs and regulatory classification as non-official drugs. As a result, the metabolic community embarked on concerted efforts to advocate for improved accessibility of life-saving medications. This involved engaging in negotiations with regulatory bodies, such as the National Organization of Drugs, to streamline the procurement process and ensure timely access to essential treatments. It was also emphasized that life-saving supplements are not merely optional but are crucial components of emergency care protocols to effectively manage metabolic crises.

Immediate access to all available drugs was considered paramount to prevent dire consequences. Specifically, peritoneal dialysis was proposed as a preferable initial approach to address acute emergencies because of its prompt implementation compared with the time-consuming process often associated with other methods such as hemofiltration (continuous veno-venous hemodialysis).

Current resources for IMD management in Greece, Cyprus and Albania are reported in Table 2.

Current and Future Challenges

Participants stated that political and administrative entities in their countries should change their approach to organizing the management of IMDs. Initiatives to foster screening programs would play a key role in gradually altering perspectives. They reported that, in other countries' experience, screening processes had impacted policymakers' views in the long term, potentially leading to incremental improvements in policy understanding. Italy's experience was cited as an example, albeit highlighting the slow pace of this progress.

Table 2. Current situation for IMD diagnosis and management.

	Genetic testing	Collaborative diagnostics	Free access to acute medications	Healthcare professionals training	Availability for international cooperation projects
Albania	Samples for genetic testing are sent abroad	Yes	No	No training processes are in place	Particular need for starting the NBS program
Cyprus	Genetic confirmation is available and free	Not routinely	No	Need to increase awareness among internists	Need for optimizing patient care and ensuring timely interventions
Greece	No national coverage; costs fall on patients	Ongoing project for external sample analysis	No	Efforts to train intensivists in acute care management and to involve internists in transition	Particular need for hemodialysis and liver transplantation support

Concerning the issue raised regarding difficulties in training other healthcare professionals to manage newborns, efforts have been made in Greece in recent years to address these tasks. Furthermore, challenges were highlighted regarding adult patients, particularly those presenting with acute decompensation in internal medicine departments. There is a pressing need to raise awareness among internists about IMDs, which can lead to metabolic decompensation.

Collaboration was initiated with university internal medicine departments to introduce these modules to young trainee doctors, emphasizing their importance in enhancing awareness and skills in effectively managing IMDs. It was further suggested that patient organizations could play a crucial role in supporting these educational efforts.

One of the major problems is the absence of a dedicated pediatric metabolic unit in Albania, Cyprus, and other Greek cities besides Athens. In addition, the absence of metabolic dietitians in these countries is highlighted as a significant priority. Collaborative initiatives primarily rely on coordination among metabolic physicians within individual centers, with limited national-level integration. Training initiatives on using hemofiltration or hemodialysis techniques for acute management were advocated as a high priority.

DISCUSSION

A panel of experts on IMDs from Greece, Cyprus, and Albania described the resources available in their countries. They outlined unmet needs and issues and discussed necessary actions and perspectives to improve screening organization and treatment accessibility (Table 3).

The participants reported that the main barriers to organizing efficient services in their countries are economic and political. Expanded NBS has recently become available in Greece, while it is absent in other countries. Drugs for emergency treatment of IMDs are not accessible to most inhabitants. NBS programs are only voluntary and not reimbursed by the national health services, limiting their relevance and effectiveness.

Medical education in the area is available in specialized centers and should be promoted to second-level professionals.

Cultural issues linked to imperfect information on the management of IMDs may impact policy decisions as treatment prospects are neglected due to the unavailability of drugs. The introduction of NBS

Table 3. Summary of results.**Albania**

- No tandem mass spectrometry technology is available in Albania nowadays.
- Previous attempt to start NBS in collaboration with Germany.
- No formal partnerships are so far in place for the diagnosis and management of IMDs.
- Genetic diagnosis for IMDs is possible by sending samples to foreign laboratories through a paid service.
- One clinical center is responsible for the management of IMDs for the country, with particular regard to Gaucher disease.

Cyprus

- Cyprus is adopting tandem mass spectrometry to expand the NBS scope, with the aim of including more conditions.
- The approach has been cautious so far, with a limited number of diseases screened since 1988. The need for expansion to capture a broader range of conditions is acknowledged since 2016 but not yet implemented.
- NBS testing is split between two laboratories, necessitating efficient coordination for sample management and processing.
- Collaboration mainly relies on informal networks and partnerships, especially with Greece and Israel, indicating room for more structured national collaboration.
- The Biochemical Genetics Department, Institute of Neurology and Genetics is the hub of the Cypriot infrastructure for diagnosing metabolic conditions, supported by specialized hospital units.
- There's a move toward building local capacity to treat acute metabolic conditions, with efforts to change pharmaceutical procurement policies for better emergency preparedness.

Greece

- The recent acquisition of a tandem mass spectrometer marks a significant step toward expanding Greece's NBS program in 2024.
- Greek specialists have engaged with international counterparts, such as those in Austria, to enhance their expertise in NBS and metabolic disorder management.
- The expansion plan includes screening for UCD, highlighting the importance of hemofiltration facilities in neonatal units for emergency cases.
- Establishing a national registry for metabolic disorders is planned to improve case management, coordination, and care.
- Initiatives are underway to create an official MetabERN (European Reference Network for Hereditary Metabolic Disorders) center, aiming to integrate and improve the care infrastructure for metabolic disorders and foster regional collaboration.

would slowly demonstrate that early diagnosis, supported by genetic testing for comprehensive diagnosis and a well-organized long-term follow-up, can enable treatment of affected children, preventing deaths, organ damage, and neurologic defects if connected with the availability of resources for long-term management^{8,9}.

Italy could be a leading example for other countries because of its long experience with NBS. A national NBS system was organized in Italy in 1992¹⁰, making screening for CHT, PKU, and CF mandatory in all newborns in Italy. A nationwide NBS program for inborn errors of metabolism was institutionalized by law between 2016 and 2017¹¹. This system includes four main functions: the screening laboratory, the laboratory for confirmatory diagnosis, clinical centers, and regional coordination/supervision. The list of screened diseases is periodically reviewed and integrated¹².

Despite the well-recognized benefits of NBS and the availability of new therapies¹³, there are still many disparities between different European countries. Historically, screening for PKU was the first NBS test introduced in the 1960s; together with CHT, they are universally screened due to their high incidence (greater than 1 in 10,000)¹⁴. The International Society for Neonatal Screening carried out a detailed analysis of NBS programs in Europe, also considering Israel, Russia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan, showing that all countries except Montenegro have introduced PKU, and all except Moldova have included CHT³. Currently, screening for CF and congenital adrenal hyperplasia is performed in about 50% of countries. Given the implementation of technologies and the availability and

effectiveness of new therapies, the NBS panel is gradually expanding throughout Europe¹⁵. Indeed, pilot projects have allowed the screening of newborns for some lysosomal storage diseases, spinal muscular atrophy, and severe combined immunodeficiency, confirming that many efforts are currently underway to further improve¹⁶⁻¹⁹. However, the choice of which diseases to screen often depends on medical and technical knowledge, the personal interests of scientists, clinicians and public healthcare professionals involved in the decision-making process, and the available funds. The improvement of the NBS panel can also be influenced in some cases by patient groups expressing their support for screening²⁰. The organization of laboratories dedicated to NBS varies widely and the communication of results also differs^{21,22}. Therefore, many steps are still needed to make progress in NBS across Europe and to carefully organize homogeneous management to improve outcomes for patients and their families.

NBS is viewed as an integrated system; various interstate collaborations are active and contacts between program managers are promoted during conferences and seminars. The International Society for Neonatal Screening has stated that rare disorders as a whole represent a substantial public health burden in Europe and that international cooperation is necessary to overcome disparities in the availability and conduct of NBS programs⁶. Additionally, databases are available for public consultation, and a close liaison between the main European organizations has recently been established²³. Thanks to collaborations between countries, it will be possible to make NBS accessible throughout Europe, hopefully with common international guidelines and shared directives. This will lead to the prompt detection of newborns potentially affected from one of the many rare diseases, helping competent local personnel to take appropriate actions and improving the state of the public health status of all European countries.

CONCLUSIONS

In conclusion, this group of authors promotes collaboration among European countries to improve the skills and culture of healthcare professionals in the area of IMD management. Cultural advancements must be transferred to the health authorities in each country. Economic resources must be gathered to make mass spectrometry, dedicated and specialized personnel for NBS screening, accessibility to emergency drugs, and structured organization for long-term management of diagnosed patients available in all European countries.

ARTIFICIAL INTELLIGENCE-ASSISTED TECHNOLOGIES:

No Artificial Intelligence-assisted technologies were used in the preparation of the article.

AUTHORS' CONTRIBUTIONS:

All the authors were involved in the study conception, and in the collection and interpretation of data, revised the manuscript and approved it before submission.

AVAILABILITY OF DATA AND MATERIAL:

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

CONFLICTS OF INTEREST:

The authors declare that they have no conflict of interest to disclose.

ETHICS APPROVAL:

Not applicable.

FUNDING:

The study received no funding.

ORCID ID:

Elena Porcù - 0000-0003-1311-1079

Anastasia Skouma - 0000-0001-6180-8335

Olga Grafakou - 0000-0003-3552-3226

Eda Postoli - 0009-0004-4783-9679.

Pascal Cullufi - 0000-0001-5678-9926

REFERENCES

1. Scarpa M, Bonham JR, Dionisi-Vici C, Prevot J, Pergent M, Meyts I, Mahlaoui N, Schielen PCJl. Newborn screening as a fully integrated system to stimulate equity in neonatal screening in Europe. *Lancet Reg Health Eur* 2022; 13: 100311.
2. Koracin V, Mlinaric M, Baric I, Brincat I, Djordjevic M, Drole Torkar A, Fumic K, Kocova M, Milenkovic T, Moldovanu F, Mulliqi Kotori V, Nanu MI, Remec Zl, Repic Lampret B, Platis D, Savov A, Samardzic M, Suzic B, Szatmari I, Toromanovic A, Zerjav Tansek M, Battelino T, Groseelj U. Current status of newborn screening in Southeastern Europe. *Front Pediatr* 2021; 9: 648939.
3. Loeber JG, Platis D, Zetterström RH, Almashanu S, Boemer F, Bonham JR, Borde P, Brincat I, Cheillan D, Dekkers E, Dimitrov D, Fingerhut R, Franzson L, Groseelj U, Hougaard D, Knapkova M, Kocova M, Kotori V, Kozich V, Kremezna A, Kurkijärvi R, La Marca G, Mikelsaar R, Milenkovic T, Mitkin V, Moldovanu F, Ceglarek U, O'Grady L, Oltarzewski M, Pettersen RD, Ramadza D, Salimbayeva D, Samardzic M, Shamsiddinova M, Songailienė J, Szatmari I, Tabatadze N, Tezel B, Toromanovic A, Tovmasyan I, Usurelu N, Vevere P, Vilarinho L, Vogazianos M, Yahyaoui R, Zeyda M, Schielen PCJl. Neonatal screening in Europe revisited: an ISNS perspective on the current state and developments since 2010. *Int J Neonatal Screen* 2021; 7: 15.
4. Loeber JG, Burgard P, Cornel MC, Rigter T, Weinreich SS, Rupp K, Hoffmann GF, Vittozzi L. Newborn screening programmes in Europe; arguments and efforts regarding harmonization. Part 1. From blood spot to screening result. *J Inherit Metab Dis* 2012; 35: 603-611.
5. Millington DS. How mass spectrometry revolutionized newborn screening. *J Mass Spectrom Adv Clin Lab* 2024; 32: 1-10.
6. Sikonja J, Groseelj U, Scarpa M, la Marca G, Cheillan D, Kölker S, Zetterström RH, Kožich V, Le Cam Y, Gumus G, Bottarelli V, van der Burg M, Dekkers E, Battelino T, Prevot J, Schielen PCJl, Bonham JR. Towards Achieving Equity and Innovation in Newborn Screening across Europe. *Int J Neonatal Screen* 2022; 8: 31.
7. Loukas YL, Soumelas GS, Dotsikas Y, Georgiou V, Molou E, Thodi G, Boutsini M, Biti S, Papadopoulos K. Expanded newborn screening in Greece: 30 months of experience. *J Inherit Metab Dis* 2010; 33 Suppl 3: S341-S348.
8. Ding S, Han L. Newborn screening for genetic disorders: Current status and prospects for the future. *Pediatr Investig* 2022; 6: 291-298.
9. Mütze U, Kölker S. Evaluierung und Optimierung des Neugeborenen Screenings mittels strukturierter Langzeitbeobachtung – am Beispiel der angeborenen Stoffwechselerkrankungen [Evaluation and optimization of newborn screening by structured long-term follow-up using the example of inherited metabolic diseases]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2023; 66(11):1249-1258.
10. Law 104/1992. <https://www.gazzettaufficiale.it/eli/id/1992/02/17/092G0108/sg> (Accessed April 2024).
11. Law 167/2016. <https://www.gazzettaufficiale.it/eli/id/2016/08/31/16G00180/sg> (Accessed April 2024).
12. Ruoppolo M, Malvagìa S, Boenzi S, Carducci C, Dionisi-Vici C, Teofoli F, Burlina A, Angeloni A, Aronica T, Bordugo A, Bucci I, Camilot M, Carbone MT, Cardinali R, Carducci C, Cassanello M, Castana C, Cazzorla C, Ciatti R, Ferrari S, Frisso G, Funghini S, Furlan F, Gasperini S, Gragnaniello V, Guzzetti C, La Marca G, La Spina L, Lorè T, Meli C, Messina M, Morrone A, Nardecchia F, Ortolano R, Parenti G, Pavanello E, Pieragostino D, Pillai S, Porta F, Righetti F, Rossi C, Rovelli V, Salina A, Santoro L, Sauro P, Schiaffino MC, Simonetti S, Vincenzi M, Tarsi E, Uccheddu AP. Expanded Newborn Screening in Italy Using Tandem Mass Spectrometry: Two Years of National Experience. *Int J Neonatal Screen* 2022; 8: 47.
13. Kelly N, Makarem DC, Wasserstein MP. Screening of newborns for disorders with high benefit-risk ratios should be mandatory. *J Law Med Ethics* 2016; 44: 231-240.
14. Bhattacharya K, Wotton T, Wiley V. The evolution of blood-spot newborn screening. *Transl Pediatr* 2014; 3: 63-70.
15. Burgard P, Rupp K, Lindner M, Haeg G, Rigter T, Weinreich SS, Loeber JG, Taruscio D, Vittozzi L, Cornel MC, Hoffmann GF. Newborn screening programmes in Europe; arguments and efforts regarding harmonization. Part 2. From screening laboratory results to treatment, follow-up and quality assurance. *J Inherit Metab Dis* 2012; 35: 613-25.
16. Burlina AB, Polo G, Salvati L, Duro G, Zizzo C, Dardis A, Bembi B, Cazzorla C, Rubert L, Zordan R, Desnick RJ, Burlina AP. Newborn screening for lysosomal storage disorders by tandem mass spectrometry in North East Italy. *J Inherit Metab Dis* 2018; 41: 209-219.
17. Angilletta I, Ferrante R, Giansante R, Lombardi L, Babore A, Dell'Elice A, Alessandrelli E, Notarangelo S, Ranaudo M, Palmarini C, De Laurenzi V, Stuppia L, Rossi C. Spinal muscular atrophy: an evolving scenario through new perspectives in diagnosis and advances in therapies. *Int J Mol Sci* 2023; 24: 14873.
18. Argudo-Ramírez A, Martín-Nalda A, González de Aledo-Castillo JM, López-Galera R, Marín-Soria JL, Pajares-García S, Martínez-Gallo M, García-Prat M, Colobran R, Riviere JG, Quintero Y, Collado T, Ribes A, García-Villoria J, Soler-Palacín P. Newborn screening for SCID. Experience in Spain (Catalonia). *Int J Neonatal Screen* 2021; 7: 46.
19. Boyarchuk O, Yarema N, Kravets V, Shulhai O, Shymanska I, Chornomydz I, Hariyan T, Volianska L, Kinash M, Makukh H. Newborn screening for severe combined immunodeficiency: The results of the first pilot TREC and KREC study in Ukraine with involving of 10,350 neonates. *Front Immunol* 2022; 13: 999664.
20. Loeber JG. European Union should actively stimulate and harmonise neonatal screening initiatives. *Int J Neonatal Screen* 2018; 4: 32.
21. Cornel M, Rigter T, Weinreich S, Burgard P, Hoffmann GF, Linder M, Loeber JG, Rupp K, Taruscio D, Vitozzi L (2011) Newborn Screening in Europe; Expert opinion document. <https://isns-neoscreening.org/wp-content/uploads/2016/06/Expert-opinion-document-on-NBS-FINAL.pdf> (Accessed May 2024).
22. Downs SM, van Dyck PC, Rinaldo P, McDonald C, Howell RR, Zuckerman A, Downing G. Improving newborn screening laboratory test ordering and result reporting using health information exchange. *J Am Med Inform Assoc* 2010; 17: 13-18.
23. Taruscio D, Piccioli A. Newborn screening in Italy: a unique program of public health in Europe. Editorial. *Ann Ist Super Sanita* 2023; 59: 1-3.