Mini-Review

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Expanded newborn bloodspot screening: developed country examples and what can be done in Turkey

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SUMMARY Bloodspot screening in newborns is an exemplary public health intervention as it is essential secondary prevention with proven efficacy and benefit for the early diagnosis and prompt treatment of rare diseases. In this mini review, newborn bloodspot screening (NBS) programs of 12 countries were examined in terms of the extent of diseases/disorders screened to form recommendations for Turkey's expanded newborn screening program. Essentially, Turkey and 11 selected countries' official policies/national programs or strategies in terms of newborn screening and the number of diseases/conditions screened were examined. The current status of spinal muscular atrophy (SMA) screening was also checked through the SMA NBS Alliance. In addition, WHO and EURORDIS guidelines for newborn screening were also reviewed. On the Pubmed database, following the search strategy "((newborn screening[Title/Abstract]) OR (newborn screening program[Title/Abstract])) OR (newborn blood spot screening[Title/Abstract])" in the PubMed database from 1 January 2008 to 1 December 2021. Diseases that will be recommended to be included in the Turkish national newborn bloodspot screening program will be presented by evaluating the updated criteria of Wilson and Jungner by constructing international comparisons. The number of diseases/disorders screened by the inspected 12 countries is eminently variable and ranges from 5 in Turkey to 51 in New York, United States of America (USA). Acknowledging the programs of other countries, it is evident that Turkey must advance its program by evaluating the epidemiological data in Turkey, the health workforce, and infrastructure while relying on the updated screening criteria. The newborn bloodspot screening program should be expanded based on the cost estimates and implemented starting with pilot applications and the diseases/disorders that are deemed appropriate should be included in the national program.

Keywords rare diseases, neonatal screening, newborn screening, dried blood spots, secondary prevention

1. Introduction

Rare diseases are a group of diseases, most of which are genetically based, chronic, mostly life-threatening, a cause of severe morbidity, and have an onset at a younger age compared to other chronic diseases (*1,2*). While at least 3–4 new rare diseases are being identified annually (*3*), there are more than 6,000 rare diseases globally identified (*4*). To include a disease in the rare disease group, frequency criteria are used corresponding to countries and regions. While diseases that affect less than 1 in 2,000 people are described as "rare diseases" in the European Union (EU) (*5*) and Turkey (*3*). It is estimated that there are 5 million individuals with rare diseases in Turkey (*3*) and 350 million globally (*6*).

Rare diseases are recognized as a serious public health issue worldwide (*7,8*). Research, diagnosis, and treatment of these diseases are exceedingly challenging and pricey. In the early stages of the disease, some can have no symptoms, are misunderstood, or confused with other diseases. Due to the lack of convenient treatment options, these diseases are seen as health orphans because they have been neglected for years (*9*).

2. As a secondary prevention: bloodspot screening in newborns and expanding of the screened disease/condition(s) list

Bloodspot screening in newborns is an exemplary public health intervention as it is an essential secondary prevention with proven efficacy and benefit for the early diagnosis and prompt treatment of rare diseases (*10,11*).

However, over time, in addition to its benefits, it has become controversial due to the cost, clinical benefit, and violation of ethical values for the diseases to be included in a screening program (*12,13*). An expert group for EU member states has stated that newborn screening should be evaluated within the framework of a common policy within the Union. Experts expressed their opinions in the following: governance of neonatal screening; criteria to evaluate whether a screening program should be performed; criteria on how a screening program should be performed; informed consent; blood spot sampling; laboratory procedures; blood spot storage; communication of positive results; confirmation of diagnosis and treatment; communication of unintended findings; quality assurance of laboratory results; screening program evaluation; epidemiological evaluation; and features of disorders, which might be considered in the gradual expansion of NBS in EU. They also created a proposed model of a decision-making matrix for an appropriate and standard policy (*14*). Expanded newborn screening programs have been initiated in the world, especially in the European Region, North America, and Australia. For this reason, this article establishes recommendations for the expansion of the current newborn blood spot screening program in Turkey, based on national data, by examining international examples.

2.1. Current status in the number of disease/condition(s) screened in newborns internationally and some countries' policy

For this mini narrative review, essentially, Turkey and 11 selected countries' official policies in terms of newborn screening and the number of diseases/conditions screened were examined. The current status of SMA screnning was also checked through the SMA NBS Alliance. In addition, WHO and EURORDIS guidelines for newborn screening were also reviewed. On the Pubmed database, following with the search strategy "((newborn screening[Title/Abstract]) OR (newborn screening program[Title/Abstract])) OR (newborn blood spot screening[Title/Abstract])" in the "PubMed" database from 1 January 2008 to 1 December 2021. A total of 2,755 articles which was the full texts accessible were evaluated, and after evaluation of the abstracts and texts, 17 articles which reflected the opinions of international consensus' and assessments, and articles examining current policies and situations of countries where official current policy documents were not available were included. Studies on diseases/conditions not currently included in the national screening program were excluded. The Wilson and Jungner criteria serve as a guide for determining whether a disease is a suitable candidate for population-wide screening (*15*) and has been used for years (*16*). However, today, because of advancements in medicine, a demand for an update has arisen. In 2008 and 2018, two different groups of researchers identified new principles (*16,17*).

Accordingly, 12 criteria were listed under 3 headlines: disease/condition, test/intervention, and program/system principles (*16*). Diseases that will be recommended to be included in the Turkish national newborn blood spot screening program will be presented by evaluating the updated criteria of Wilson and Jungner by constructing international comparisons.

The national newborn blood spot screening programs of 12 countries (Australia, Canada, Germany, Denmark, United Kingdom (UK), Israel, Italy, the Netherlands, New Zealand, Norway, Turkey, and United States of America (USA) were examined.

2.2. Current situation in the number of diseases/conditions screened in 12 countries

The number of diseases/disorders screened by the 12 countries is highly variable and ranges from 5–51. The number of diseases/conditions screened are as follows: 32 in Australia (*18*), 25 in Ontario, Canada (*19*), 19 in Germany (*20-22*) 19 in Denmark (*22,23*), 9 in the UK (*24*), 12 in Israel (*25*), 40 in Italy (*26*), 25 in the Netherlands (*27*), 26 in New Zealand (*28*), 26 in Norway (*29*), 5 in Turkey (*30*) and 51 in the New York, USA (*31*).

The most frequently screened diseases in the 12 countries examined are as follows: phenylketonuria (PKU) and congenital hypothyroidism (n = 12); cystic fibrosis, glutaric acidemia type I, maple syrup urine disease, and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (n = 11); isovaleric acidemia and very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD) (n = 10); congenital adrenal hyperplasia, biotinidase deficiency, tyrosinemia type 1, methylmalonic acidurias, propionic acidaemia and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) (n = 9); severe common immun deficiency (n = 8); galactosemia, carnitine palmitoyltransferase-I (CPT-I) deficiency and homocystinuria and trifunctional protein (TFP) deficiency (n = 7); (multiple) holocarboxylase synthetase deficiency homocystinuria, carnitine acylcarnitine translocase (CACT) deficiency and carnitine palmitoyltransferase-II (CPT-II) deficiency (n = 6). Additionally, 33 diseases/disorders are screened in 1, 2, 3, 4, or 5 countries (Table 1, Online Data, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=100*).

3. Differences between countries and international standards

When the newborn blood spot screening programs of these 12 countries is examined in terms of the number of diseases/disorders screened, the New York, USA ranks first with 55 diseases/conditions, Turkey ranks last with 5 diseases/disorders followed by the UK with 9 diseases/disorders. Additionally, among the examined countries, Italy ranks first with 40 diseases/disorders

screened in the member countries of the World Health Organization Regional Office for Europe. However, New York, USA has the highest number of screened diseases/disorders with 54 diseases/disorders among the examined countries. The disease, commonly screened for in all of the examined countries, is PKU. The striking finding is that Turkey is the only country among these 12 countries that does not screen for glutaric acidemia type 1, maple syrup disease, and MCAD deficiency, and also one of only two countries that do not screen for isovaleric acidaemia and VLCAD deficiency. The prevalence of consanguineous marriages in Turkey is around 25% (*32*) where consanguineous marriages are a risk factor for rare diseases. Therefore, there is a demand for an expanded newborn blood spot screening program that will not only use strategies to reduce consanguineous marriages, but also provide early diagnosis and treatment of affected children born from existing marriages. EURORDIS, funded by the EU and brings together rare diseased individuals and patient associations, has recently announced that Italy has the largest newborn blood spot screening program in Europe and called for a similar program to be put on the agenda in other countries (*2*).

3.1. Rare diseases screened in newborns in Turkey from past to present and future plans

Newborn screenings in Turkey started with PKU in 1983 and became a national program in 1994. Subsequently, congenital hypothyroidism was included in the National Screening Program in 2006, biotidinase deficiency in 2008, and cystic fibrosis in 2015, respectively (*30,33*). Finally, the congenital adrenal hyperplasia screening program was started in 2017 (*30*). gradually expanding and becoming national at the beginning of 2022. Approximately 1.2 million babies were born in Turkey in 2020. Currently, there are two National Screening Laboratories. Heel blood is taken within 48-72 hours after birth and results are obtained in 1-2 days on average. It has been stated that the coverage is 97% (*34*).

It is stated in the "Report of the Parliamentary Research Commission Established to Determine the Treatment and Care Methods for ALS, SMA, DMD, MS and Other Diseases with No Definitive Treatment, and the Problems and Solutions of People with These Diseases and Their Relatives", under the Turkish Grand National Assembly, that it is planned to screen an additional 32 diseases which were reported to the commission by the Ministry of Health, General Directorate of Public Health (Table 2) (*35*). If the screening program in Turkey can be expanded with these diseases/disorders, it may develop into one of the most extensive screening programs in the world.

3.2. Opinions of various authorities and institutions/organizations regarding the updated newborn screening criteria

By examining the screening criteria put forward by Wilson and Jungner in 2018, 12 principles under 3 domains were determined and thus updated (*16*). Accordingly, the first domain consists of 3 parts: disease/condition principles *a*) epidemiology of the disease or condition, *b*) natural history of the disease or condition, *c*) target population for screening. The second domain is test/intervention principles, and again consists of 3 parts: *a*) screening test performance characteristics, *b*) interpretation of screening test results, *c*) post-screening test options. The last and third domain, program/system principles, consists of 6 parts: *a*) screening program infrastructure, *b*) screening program coordination and integration, *c*) screening program acceptability and ethics, *d*) screening program benefits and harms, *e*) economic evaluation of screening program, *f*) screening program quality and performance management (*16*).

Additionally, EURORDIS identified 11 key principles for newborn screening in January 2021 (36). These principles can be briefly explained as follows: *i*) screening should be primarily for disease/conditions that can be acted upon, such as treatment, *ii*) neonatal blood spot screening should be embedded within the national system so that it is accessible, *iii*) families of the affected babies diagnosed after the screening should be provided with psychological, *iv*) social and economic support by compatible experts, and all stakeholders should be included in the screening program, *v*) in order to expand the screening program, it should be susceptible to clear, transparent, independent, evidence-based information and policy change and development, *vi*) the management of the screening program should be clear, comprehensive, transparent and accountable, *vii*) the expenses should be considered while determining the diseases to be included or not in the screening program but it should not be conclusive, and should be in line with the most recent evidence, *viii*) all stakeholders should be informed and educated about rare diseases and the screening program, *ix*) the process should be standardized for Europe in terms of quality and uniformity, *x*) blood spot samples should be stored in the national biobank for research purposes, holding appropriate security measures, *xi*) ERN affiliated centers should be integrated into the care and should be considered as preferential partners in providing recommendations on the screening policies.

3.3. Importance, benefit, necessity and limitations of the newborn screening

Newborn blood spot screening has some advantages and disadvantages. These should also be considered when determining the diseases/disorders to be screened (*37,38*). Expanded newborn screening programs have been shown in various studies to be cost-effective, affect the quality of life, and reduce mortality and morbidity (*39*). Lindner *et al*. (*10*) evaluated the expanded newborn blood spot screening in Germany and found that physical and

Table 2. Diseases/Conditions Planned to be Included in the Screening Program of the Ministry of Health, General Directorate of Public Health in Turkey

Disease/Condition Groups	Diseases/Conditions
Fatty Acid Oxidation Disorders	• Medium chain acyl CoA dehydrogenase deficiency • Long chain acyl CoA dehydrogenase deficiency • Short chain acyl CoA dehydrogenase deficiency • Multiple acyl CoA dehydrogenase deficiency (Glutaric acidemia type II) • Long chain hydroxyacyl CoA dehydrogenase deficiency • Trifunctional protein deficiency
Carnitine Cycle Disorders	• Carnitine transporter deficiency • Carnitine palmitoyl transferase I deficiency • Carnitine palmitoyl transferase II deficiency • Carnitine/acyl carnitine translocase deficiency
Organic Acidemias	• Methylmalonic acidemia • B-ketothiolase deficiency • 3-OH-3-methylglutaryl-CoA lyase deficiency • 3-methylcrotonyl-CoA carboxylase deficiency • Isovaleric acidemia • 3-methylglutaconyl-CoA hydratase deficiency • 2-methylbutyryl-CoA dehydrogenase deficiency • Isobutyryl-CoA dehydrogenase deficiency • Propionic acidemia • Glutaric acidemia type I • 3-oxothiolase deficiency • Holocarboxylase deficiency
Urea Cycle Disorders	• Argininosuccinate synthetase deficiency (Citrullineemia) • Argininosuccinate lyase deficiency (Argininosuccinic aciduria) • Arginase deficiency
Amino Acid Disorders	• Tetrahydrobiopterin deficiencies • Maple Syrup Urine Disease (MSUD) • Tyrosinemia • Homocystinuria • Cobalamin disorders • Methylenetetrahydrofolate deficiency

*Congenital Adrenal Hyperplasia**

* The screening program of congenital adrenal hyperplasia has been extended nationally since 2022.

Source: (*35*)

cognitive benefits were similar when phenylketonuria was taken as the gold standard. In addition to screening, positive cases have access to diagnostic tests and, as a result, they also have access to appropriate treatments. In this sense, it is critical to evaluate the diseases/disorders to be screened in terms of long-term outcomes (*40*). According to the long-term evaluation at Boston Children's Hospital, the expanded blood spot screening program had increased the mean IQ score and severe clinical outcomes were significantly reduced, indicating the success of the program (*41*). Early diagnosis of some of these conditions where treatment is available is additionally of great importance (*42*). In addition to the mentioned benefits, it is probable to claim that screening has some negative aspects. Since they are not diagnostic, screening tests have a certain percentage of false positives or false negatives, which should be within the limits of society's acceptance. While false-positive results cause unnecessary additional testing and thus additional costs, redundant intervention, and complications for the patient, false-negative results may cause delays in the diagnosis (*37,38*). Another critical problem with screening is the demand for a significant health workforce and infrastructure (*38*).

3.4. A holistic view of public health in screening for rare diseases in newborns

The approach to rare diseases that are planned to be screened with a holistic approach and public health principles is given in Table 3. Although it is difficult to calculate the burden of rare diseases, it is known that childhood is an important cause of mortality and morbidity. It has been shown that of all inborn errors of metabolism, which are mostly covered by neonatal screening programs, the overall birth prevalence estimate was 50.9 per 100,000 live births by Water *et al*. (*43*). It is stated that the inborn errorrs of metabolism are especially responsible for sudden infant deaths and that most of them are diseases that can be screened and treated (*44,45*). In this sense, the issue cannot be seen apart from Sustainable Development Goals (SDG) Goal 3, Target 3.2 which is explained (*46*) "By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5

Table 3. The holistic approach with the principle of public health on screening

Disease Onset and Progression				
Preclinic Phase		Clinic Phase	Postclinic Phase	
Primordial prevention	Primary prevention	Secondary prevention	Tertiary prevention	Quadruple prevention
Evaluation of social determinants of rare diseases that are planned to be screened	Defining the risk factors	Reduction and prevention of delay in diagnosis (early diagnosis)	Social and medical rehabilitation	Avoiding fragmented service delivery
Making the infrastructure ready	Planning the intervention for preventive strategy	Providing appropriate, effective and timely treatment options	Interventions to reduce complications and slowdown the prognosis	Avoiding overdiagnosis
Legal regulations	Intervention	Standardization of the treatment protocol		Avoiding overmedication or medical/surgical intervention
		Integration of the decision support systems		Integration of health information systems

Sustainable Development Goal 3, Target 3.2: By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births. From the data to policy; epidemiological assessment and monitoring for all phases and strategies, integrity of society, national/international solidarity, public health ethics, equity in health and social care in the context of universal health coverage, financial planning, management of the health workforce, training of healthcare professionals, and establishing the appropriate infrastructure.

mortality to at least as low as 25 per 1,000 live births". Although screening is a secondary prevention strategy, it may be incomplete unless complemented by the other four prevention strategies (*38,47*). To give an example from social determinants, the existence of isolated groups in a society *e.g.* populations with frequent consanguinity marriages may cause some rare diseases to be seen frequently (*43*). Also, screening of hemoglobinopathies such as hemophilia, thalassemia and fragile X syndrome, as well as CF in risky groups; in addition, Tay-Sachs disease, Canavan disease, Familial dysautonomia for Ashkenazi Jews is recommended by Joint SOGC–CCMG Committee (*48*). Also Tay-Sachs disease carrier screening is recommended by the American College of Obstetricians and Gynecologists (ACOG) for women with Ashkenazi Jewish, French-Canadian or Cajun ancestry (*49*).

4. Limitations

This review cannot be considered as a systematic review. It has some limitations, notably at the level of evidence. The limited number of countries examined and the fact that the countries examined are mostly developed countries may be considered as cause for bias. The small and insufficient number of studies conducted in Turkey has made it difficult to evaluate the specifics of the country and therefore caused the recommendations to become limited.

5. Conclusion

The future of newborn screening programs, as an example of secondary prevention, seems to be an important issue that will always find its place in the scientific community, to conserve and build up its emphasis in terms of public health.

In order to achieve the determined goals of sustainable development without wasting time, equitable access to health services should be ensured by considering ethical principles. When current criteria are taken into consideration and examined, it is obvious that an assessment must be made about expanding the newborn blood spot screening program. In this scheme, the epidemiological information, the infrastructure of the screening program, and the economic evaluation of the screening program should especially be scrutinized about rare diseases/conditions that are candidates for screening in Turkey. To begin with, the establishment of a rare disease registry information system in Turkey would provide epidemiological information and outputs such as incidence rate for screening, benefits from treatments and their effects on survival rate, and thus, a hierarchy from data to information to policy. Second, infrastructure projects must be arranged for the expanded screening program, pilot applications can be implemented if necessary, and an appropriate budget should be allocated.

Thirdly, screening programs should be piloted as means of evaluating economic outcomes. Finally, it is evident that there is a need for more studies on the subject in most investigated countries, especially Turkey and they should review their policies in the context of a holistic approach with the principle of public health on screening.

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