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Newborn Screening: From the Past to the Future

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June 28, 2022, the second anniversary of International Newborn Screening Day was celebrated despite ongoing negative impact of Covid-19 pandemic.[1] June 28, originally dates back to the birthday of Dr. Robert Guthrie (June 28, 1916). Dr. Guthrie was a microbiologist who, as the father of a mentally retarded child and uncle of a niece with PKU, dedicated his life to raising awareness of the need for newborn screening for treatable diseases after introducing a new bacterial inhibition test using dried blood spots on filter paper cards to screen newborns for phenylketonuria.

Screening was first defined by the Commission on Chronic Illness in 1957 as "the presumptive identification of an undiagnosed disease or defect through the use of tests, examinations, or other procedures that can be rapidly applied." However, it was not until 1968 that the screening principles were defined by Wilson and Jungner.[2] These ten principles were the main basis for development of screening policies that took into account prevalence, diagnosis and treatment, cost of case finding, etc., in order to include an ever-growing list of diseases in national programs.

The goal of newborn screening is early detection and treatment of all newborns with treatable conditions that otherwise cause both mortality and morbidity, in the early presymptomatic period. These conditions include inborn errors of metabolism (IEM), endocrine disorders, hemoglobinopathies, immunodeficiencies, cystic fibrosis, infectious diseases such as HIV and CMV, and critical congenital heart defects. Although NBS is absolutely lifesaving and accepted worldwide, the structure of NBS programs varies, and there is no consensus on the selection of diseases for expanded screening programs between countries and even between regions within a country.[3] The ethical issues associated with potentially equivocal findings and late-onset diseases for which there is no clear evidence on when and how to initiate therapy are a burden in the application of a universal newborn screening program. Each country is independently governed and makes its own decisions which disease to include in the NBS. Today, the known percentage of newborns screened is 100% in the United States, 78% in Europe, 32% in Latin America, 26% in the Middle East and North Africa, 13% in Asia-Pacific, and 0% in Central Africa. The financial situation of countries is one of the major barriers to newborn screening, although not the main reason for heterogeneity.

Newborn screening has become the most successful program for secondary prevention of IEM.[4] The first efforts to screen for IEM began in the 1930s with the detection of a biomarker, phenylpyruvic acid, in the urine samples of patients with phenylketonuria. However, the major breakthrough was Guthrie's development of a simple and inexpensive bacterial inhibition assay to detect phenylalanine levels using dried blood samples.[5] This important step was followed a few years later by the development of a radioimmunochemical method for the detection of congenital hypothyroidism. While the number of disorders studied, including IEMs, was initially limited, the panel was gradually expanded in the mid-1990s to early 2000s when tandem mass spectrometry (MS/MS) became available and was used to detect biochemical genetic disorders.[6] This was a revolutionary step because TMS-based techniques allowed multiplex screening of different metabolites and different diseases in the same run using the same sample, changing the "one sample-one disease" rule to "one

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sample-multiple diseases." The introduction of MS/MS into the NBS allowed screening for 40-50 diseases with a single blood sample. The low rates of false positives and false negatives also made TMS screening cost-effective and highly efficient. On the other hand, the number of diseases that can be screened simultaneously with the same method MS/MS is still limited, and the chemical properties of the different metabolites favor the diagnosis of certain diseases over others.[7]

Despite increasing technical capabilities, these drawbacks have prevented most human diseases from being included in the NBS program and have led to a search for new alternatives for newborn screening. The advent of next-generation sequencing (NGS) in the form of whole-exome and whole-genome analyzes has led to attempts to expand the use of DNA sequencing in NBS to improve diagnostic and prognostic utility. Several key features of NGS make it a potentially powerful technology for NBS. These techniques have the advantage of high throughput; a single test can be used for a range of diseases with simultaneous analysis of a large number of genetic loci, even beyond the range of congenital defects, regardless of whether a biochemical marker is available. As the cost of sequencing steadily decreases, many researchers consider NGS more feasible for newborn screening.[8]

However, the transition to genetic diagnostics in newborn screening requires overcoming major logistical and ethical hurdles. NGS, particularly whole exome sequencing (WES)/whole genome sequencing (WGS), will provide large amounts of data that must be properly analyzed and interpreted.[9] Interpretation of the data also remains controversial, particularly in addressing variants of unclear significance and deciding whether they are benign, pathogenic, likely benign, or likely pathogenic. Despite the health benefits of genomic testing in the clinical setting, the performance of comprehensive genetic testing in asymptomatic infants is widely controversial, primarily because of concerns about psychological and physical harm (e.g., risks associated with interventions and parental fear of positive findings, especially for conditions without current treatment.[10,11]

In Turkiye, the estimated prevalence of inborn errors of metabolism and many other genetic diseases is high compared with other countries, partly due to the high rate of consanguineous marriages, which is as high as 20-25% in some regions.[12,13] Phenylketonuria, maple syrup urine disease (MSUD), methylmalonic acidemia (MMA), hereditary urea cycle defects (UCD), and galactosemia are estimated to be the most commonly observed metabolic disorders.[14,15] The birth prevalence of hyperphenylalaninemia was reported to be 1:4192, PKU 1:5059, biotinidase deficiency 1:11763, and galactosemia 1:23775 in Turkey.[14-17]

The history of the NBS program began in 1986 after the high prevalence of phenylketonuria was noted in a pilot study in 1983.[16] Biotinidase deficiency, hypothyroidism, cystic fibrosis, and finally congenital adrenal hyperplasia were added to the nationwide NBS program in 2006, 2008, 2015, and 2021, respectively.[18-20] Although the studies showed a high prevalence of IEMs detected by both selective and nonselective screening using MS/MS in Turkey, an extended NBS using MS/MS was started in 2002 by private initiatives and some college hospitals, but unfortunately it is still not part of the nationwide NBS program.[21-24]

In summary, we are not even on the threshold of a global NBS program, but every newborn has the right to be screened for preventable diseases that can be detected by simple NBS techniques, and it is the duty of governments to provide these health services to the public.

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