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Newborn screening in Mexico and Latin America: present and future

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Abstract

The first newborn screening (NBS) program to be implemented in Latin America was in Mexico in 1974, eleven years after the initial NBS programs in other parts of the world. In the last 50 years, progress has been made in implementing and expanding NBS in Mexico and across Latin America, yet children across the region do not fully benefit from this effective public health strategy. Here, we review the progress in the implementation of expanded NBS in Latin America with a focus on Mexico and the challenges faced by its complex healthcare system. In light of new technologies such as genomic sequencing and their potential utilization for NBS, we discuss what the future of NBS may be for Mexico and countries in Latin America and the Caribbean region, given economic and technological constraints.

Keywords: Neonatal screening, NBS, ENBS, gNBS, genetic diseases, early diagnosis, precision health

THE PAST AND PRESENT OF NEWBORN SCREENING IN MEXICO AND LATIN AMERICA

Newborn screening (NBS) is a public health strategy aimed at identifying, in the first days of life, serious conditions that may affect the survival or health of a child, and where early diagnosis and treatment result in improved health outcomes, thus reducing morbidity, disability, and mortality. Although established in 1963 with the first mandated screenings done for phenylketonuria (PKU) in the United States, the implementation of NBS around the world is very heterogeneous. In Latin America, the implementation of NBS programs is unequal and inconsistent. Only 16 of the 33 countries in the region currently have a national NBS program and the number of conditions included varies widely across countries from one condition, namely congenital hypothyroidism (CHT) being screened in 16 countries, up to 29 conditions screened for in Costa Rica [Table 1][1,2]. The development of tandem mass spectrometry (MS/MS) technologies enabled the screening of dozens of metabolites in a single assay, expanding the capabilities of classical biochemical NBS to include disorders of the metabolism of amino acids, organic acidemias, and fatty acid oxidation disorders[3]. Unfortunately, the adoption of MS/MS technologies for expanded newborn screening (ENBS) in Mexico and Latin America is still lagging behind by decades, with only Costa Rica and Uruguay having national ENBS programs in the region[1,2] and a few regional, state, or localized efforts in a handful of countries. Economic conditions, outdated legislation and technology, and limitations on coverage and accessibility have hindered the widespread adoption of NBS in the Latin American and Caribbean (LAC) region. This has resulted in a considerable number of infants with rare diseases going undiagnosed and untreated, resulting in preventable morbidity and mortality in these populations.

In Mexico, NBS was first implemented in 1974, being the first country in Latin America to adopt this public health strategy to screen infants for PKU, CHT, and congenital toxoplasmosis. Due to technical difficulties with the assay, testing for toxoplasmosis was dropped shortly after, whereas initial screening results for PKU and CHT showed the success of the program. In 1977, the NBS program was paused, but reinstated in 1986. In 1988, legislation was approved to make NBS mandatory in medical institutions nationwide for newborns. However, despite the evidence supporting the importance of screening for PKU, this disorder was also removed from the program due to the low number of positive cases detected in the Mexican population, leaving the national NBS program to screen only for CHT[4]. In 1998, the national NBS program was expanded to include PKU, congenital adrenal hyperplasia (CAH), galactosemia (GAL), and biotinidase deficiency (BTD) for all newborns in Mexico. Updated guidelines published in 2002 suggested the expansion of NBS to test for additional disorders based on the recommendations of the National Center of Epidemiological Surveillance (Centro Nacional de Vigilancia Epidemiológica); however, no official mandate was established. New guidelines were published in 2012, emphasizing the importance of the expanded metabolic newborn screening covering at least CHT, CAH, GAL, disorders of amino acid metabolism, disorders of fatty acid metabolism, cystic fibrosis (CF), hemoglobinopathies, severe combined immunodeficiency (SCID), and leaving the possibility open to include other disorders that represent a public health problem. In January 2013, a Congress decree was published, establishing the mandatory implementation of ENBS and ophthalmological screening for all Mexican newborns, as well as retinal and hearing screening for premature newborns, to ensure integral childhood development and the prevention and detection of hereditary and congenital conditions. Despite this, ENBS is still not implemented nationally and the major public healthcare institutions continue to screen for only six conditions: CHT, PKU, CAH, CF, GAL, and glucose-6-phosphate dehydrogenase deficiency (G6PDD)[2,4,5]. Individual institutions and healthcare systems can include additional conditions to screen for based on their budget, their technological and logistical capabilities, and other internal considerations as determined by institutional review committees.

Table 1. Newborn screening programs in Latin American countries

LATAM country	Year first implemented	Current number of conditions included in screening	Public/private access/implementation
México	1974	Screening of 6 to 76 disorders is variable depending on the healthcare system. Main conditions screened for include CHT, PKU, CAH, CF, GAL, BTD, and G6PDD	Public nationwide mandated; public/private ENBS options, a variable number of conditions depending on institution or state
Argentina	1986	Screening for 6 disorders (CHT, PKU, CAH, CF, GAL, BTD)	Public nationwide mandated. Some cities screening for additional disorders
Bolivia	2006	Screening for 4 disorders (CHT, PKU, CAH, and CF). Only CHT is mandated nationwide	Public nationwide mandated but variable per region
Brazil	2001	Screening for 6 conditions (CHT, PKU, CAH, CF, BTD, and Hemoglobinopathies)	Public nationwide. ENBS for metabolic disorders available in some states
Chile	1992	Screening for 2 conditions (CHT and PKU)	Public. ENBS pilot undergoing to expand to 26 conditions
Colombia	2000	Only CHT is screened for nationwide. PKU, CF, GAL, BTD, CAH and Hemoglobinopathies added in 2019 as part of the basic NBS program	Public nationwide mandated; private options available including additional conditions. ENBS pilot program being evaluated to screen for 33 total disorders
Costa Rica	1990	Screening for 29 conditions including CHT, PKU, CAH, CF, GAL, Hemoglobinopathies, MSUD, other amino acid disorders, fatty acid oxidation disorders, and organic acidurias	Public nationwide mandated. Most comprehensive public program in LATAM
Cuba	1986	Screening for 6 disorders (CHT, PKU, CAH, GAL, CF, BTD)	Public nationwide
Ecuador	2011	Screening for 4 disorders (CHT, PKU, CAH, GAL)	Public nationwide
El Salvador	2008	Only screening for CHT	Regional public program
Honduras	2016	Screening for 5 disorders (CHT, PKU, CAH, GAL, CF)	Public with variable coverage
Panamá	2007	Screening for 8 disorders (CHT, PKU, CAH, GAL, CF, Hemoglobinopathies, Sickle cell disease, G6PDD)	Public nationwide mandated
Paraguay	2004	Screening for 3 disorders (CHT, PKU, CF)	Public nationwide
Perú	2012	Screening for 5 disorders (CHT, PKU, GAL, CAH, CF)	Public nationwide
Uruguay	1994	Screening for 28 disorders including CHT, PKU, CAH, CF, Hemoglobinopathies, and additional 23 metabolic conditions including MSUD, other amino acid disorders, fatty acid oxidation disorders, and organic acidurias	Public nationwide Among the most comprehensive public programs in LATAM
Venezuela	1999	Screening for 2 disorders (CHT, PKU)	Public nationwide

NBS: Newborn screening; ENBS: expanded newborn screening; CHT: congenital hypothyroidism; PKU: phenylketonuria; MCADD: medium-chain acyl-CoA dehydrogenase deficiency; CF: cystic fibrosis; GAL: galactosemia; CAH: congenital adrenal hyperplasia; BTD: biotinidase deficiency; MSUD: maple syrup urine disease; G6PDD: glucose-6-phosphate dehydrogenase deficiency.

The Mexican healthcare system is complex and fragmented, with multiple public healthcare providers serving different fractions of the population according to their employment affiliation or lack thereof. A child born in Mexico will receive medical care, including NBS, depending on the employment affiliation of their parents. Petroleos Mexicanos (PEMEX) is the Mexican national oil company and it has a network of hospitals and clinics across the country that is available to workers of the company and their families and serves about 1.2% of the Mexican population. The PEMEX Genetics Department has since 2005 implemented the most comprehensive public metabolic ENBS program in Mexico with the screening of 69 conditions initially through MS/MS, and later in 2012 with the expansion to 76 inborn errors of metabolism (IEM) disorders, SCID, and six lysosomal storage disorders (LSDs), namely Fabry, Gaucher, Pompe, Krabbe, Hurler, and Niemann-Pick diseases[6]. Between January 2005 and December 2019, PEMEX screened 65,600 newborns born within their hospital system. Of those, 806 newborns were found to have a positive screen test by ENBS and confirmed to have a genetic disorder. Of these, 779 were confirmed to have an inborn error of metabolism, 25 were positive for a lysosomal storage disorder, and 2 were found to have a congenital immunodeficiency[7]. G6PDD was the most commonly identified condition (1 in 178 newborns), followed by transient neonatal tyrosinemia (TNT, 1 in 194 newborns). A positive screening

result for any of the six lysosomal storage conditions was obtained in 1 in 1,212 newborns and CHT was identified in 1 in 2,128 newborns. The most frequent lysosomal storage disease identified by ENBS was Pompe pseudodeficiency, followed by late-onset renal Fabry disease due to a founder variant (p.Arg363His) in the *GLA* gene in the Mexican population[7]. Early identification of newborns with these conditions through the ENBS program at PEMEX has enabled improved disease management and timely therapeutic interventions through dietary substitution and supplementation, with positive outcomes observed through longitudinal follow-up at PEMEX.

Healthcare services for military members and their dependents are provided by either SEDENA (Secretaría de la Defensa Nacional) or for navy members by the SEMAR (Secretaría de Marina). Both of these institutions have implemented ENBS and screened newborns for more than 60 conditions as part of their programs. Results of SEMAR's ENBS program showed a prevalence of 1 in 651 newborns with a genetic disorder in their population, with an ENBS coverage of 99.4% of all births in their system. The most prevalent conditions detected were G6PDD, followed by CHT and CAH[8].

Since 2019, the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), one of the major public healthcare systems in Mexico that serves State workers and their families throughout the country, has implemented ENBS for 66 analytes and currently screens for 78 conditions. Disease prevalence and findings to date for ISSSTE's ENBS program have not been published yet. The other two major public healthcare systems, Instituto Mexicano del Seguro Social (IMSS) and Secretaría de Salud (SS), which serve the great majority of the Mexican population, screen for 7 and 6 conditions, respectively [Table 2].

More recently, advocacy efforts from the civil society, clinicians, and researchers have achieved the implementation of ENBS in Mexican states beyond specific healthcare systems. The Mexican state of Quintana Roo legislated in 2021 the implementation of ENBS for all newborns born in that state, while most recently, in 2023, the state of Guanajuato followed suit[9,10]. Although similar to the national ENBS guidelines, these reforms to the state health laws do not explicitly mention the number or list of conditions to be screened for; however, the inclusion of ENBS as part of individual state health laws is important to achieve national implementation. Additionally, since 2022, National Newborn Screening Day has been officially recognized in Mexico every June 28th to raise awareness and increase education about it in the country. Most recently and as part of these efforts to increase awareness and achieve improved implementation and coverage, effective from July 2023, results for the five types of newborn screening mandated for Mexican newborns, namely metabolic, hearing, visual, cardiac, and hip dysplasia, will be included in the national vaccination card for all infants born in Mexico [Figure 1][11]. The national vaccination card is an official government-issued document that tracks early development, wellness, and the application of compulsory immunizations for children born in Mexico from 0 to 9 years of age. Of the mandated screenings, only metabolic NBS/ENBS involves molecular confirmatory testing, while the other types of screening are merely clinical and, similar to metabolic NBS, are not implemented consistently and widely. Therefore, inclusion and mandatory report of results for these screenings are relevant to achieve homogenization in the implementation of NBS across the healthcare institutions in Mexico, and ensure that NBS is being performed for every infant born in the country regardless of parents' employment or healthcare provider affiliation.

The estimated coverage of basic NBS in Mexico was about 84% in 2018[1]; however, a major disruption and suspension of NBS occurred in 2019 due to problems with the Ministry of Health contracting in twelve Mexican states. Although only newborns born in hospitals and medical units around the country are screened, the uptake for institutional births is high in Mexico (> 90%), but this varies among states[12], with a

Table 2. Major Mexican public healthcare providers and number of conditions that are screened for in their respective NBS/ENBS programs

Healthcare provider	Births in Mexico (%)	NBS/ENBS program	Number of conditions screened
PEMEX	0.2%	ENBS (2005)	83 (76 IEMs, SCID, LSDs, Hemoglobinopathies)
SEDENA	0.5%	ENBS	> 60 conditions (IEMs, Hemoglobinopathies)
SEMAR	0.1%	ENBS	> 60 conditions (IEMs)
ISSSTE	2.0%	ENBS (2019)	78 (IEMs)
IMSS	37%	NBS	7 (CHT, CAH, PKU, BTD, GAL, CF, G6PDD)
SS	57%	NBS	6 (CHT, CAH, PKU, GAL, CF, G6PDD)

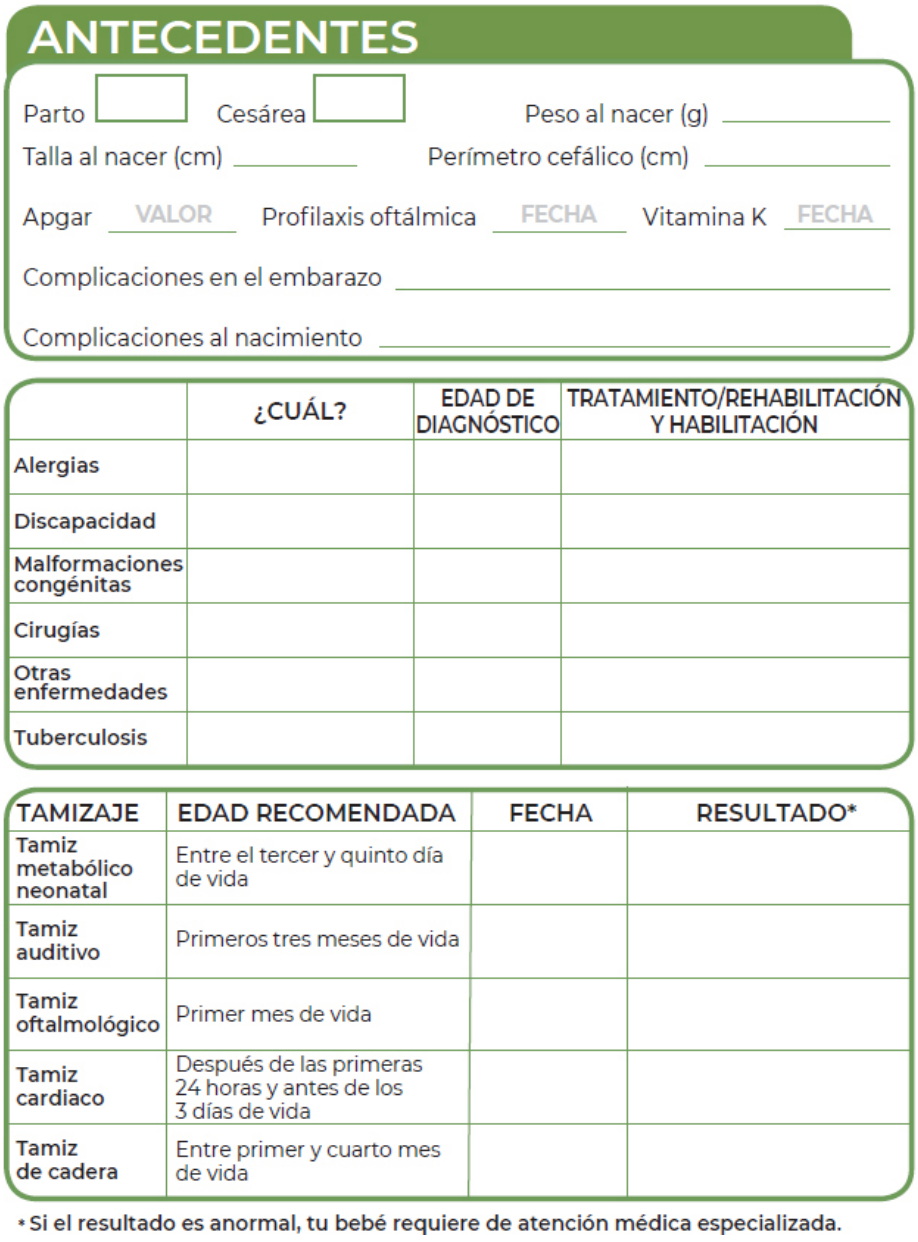
NBS: Newborn screening; ENBS: expanded newborn screening; CHT: congenital hypothyroidism; PKU: phenylketonuria; CF: cystic fibrosis; GAL: galactosemia; CAH: congenital adrenal hyperplasia; BTD: biotinidase deficiency; G6PDD: glucose-6-phosphate dehydrogenase deficiency.

fraction of newborns born at home, especially in rural areas. The approximate prevalence of 1 in 90 newborns identified with a confirmed actionable genetic inborn disorder through ENBS, highlights the need to implement expanded newborn screening programs for early disease diagnosis and management effectively across the country.

THE IMPORTANCE OF EARLY DIAGNOSIS

The importance of an early diagnosis to enable proper clinical and therapeutic management cannot be overstated. Ideally, NBS/ENBS will detect a biochemical and subsequent molecular defect in the first days of life and early enough to enable a timely intervention preventing long-term disability and mortality. A recent report from a national tertiary medical center in Mexico showed that only 35.4% of children ascertained for having an IEM detectable by ENBS had been screened at birth. Furthermore, these patients had an average diagnosis time of 4 months, which is too late to intervene for many IEMs with available interventions[13]. In contrast, ENBS programs that can detect disorders early enough and provide appropriate management and treatment are observing improved outcomes for patients with IEMs and LSDs[6,7].

Another dramatic example of the importance of early diagnosis and intervention is the recent introduction of newborn screening for Spinal Muscular Atrophy (SMA) in some countries. The emergence of novel molecular therapies for this condition, such as gene replacement via adeno-associated viral vectors (AAVs) and splicing modifying molecules, has transformed the prognosis of a condition that, if untreated, results in 90% of patients being dependent on permanent mechanical ventilation or dying within the first 2 years of life. In the last few years, three therapies have been developed and approved to treat SMA by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), while additional therapies are still in development[14]. In Mexico, the Federal Commission for Sanitary Risk Protection (Comisión Federal para la Protección de Riesgos Sanitarios, COFEPRIS) is the approving body for new drugs and therapeutics. The three available treatments for SMA are approved by COFEPRIS, but they are not necessarily available to patients in the country and their cost is prohibiting for most families. Moreover, in all cases, therapeutic success depends on the administration of the drugs at the earliest possible age and this is only possible through early diagnosis, which can be facilitated by NBS. Among SMA patients with two copies of the paralogue gene *SMN2*, 78% achieved independent walking when treated with a disease-modifying therapy within the first 30 days of life, in comparison with 25% and 8% for those treated between 31 to 90 and after 90 days, respectively. Early intervention showed an even greater impact on motor skill development in patients with three copies of *SMN2*, with 100%, 86% and 31% of children walking by themselves when treated within the same ranges described before[15].



ANTECEDENTES

Parto ☐ Cesárea ☐ Peso al nacer (g) _____

Talla al nacer (cm) _____ Perímetro cefálico (cm) _____

Apgar VALOR Profilaxis oftálmica FECHA Vitamina K FECHA

Complicaciones en el embarazo _____

Complicaciones al nacimiento _____

	¿CUÁL?	EDAD DE DIAGNÓSTICO	TRATAMIENTO/REHABILITACIÓN Y HABILITACIÓN
Alergias			
Discapacidad			
Malformaciones congénitas			
Cirugías			
Otras enfermedades			
Tuberculosis			

TAMIZAJE	EDAD RECOMENDADA	FECHA	RESULTADO*
Tamiz metabólico neonatal	Entre el tercer y quinto día de vida		
Tamiz auditivo	Primeros tres meses de vida		
Tamiz oftalmológico	Primer mes de vida		
Tamiz cardiaco	Después de las primeras 24 horas y antes de los 3 días de vida		
Tamiz de cadera	Entre primer y cuarto mes de vida		

*Si el resultado es anormal, tu bebé requiere de atención médica especializada.

Figure 1. Example of the page that includes newborn screening results in the national vaccination card in Mexico since 2023. Parents of newborns in Mexico receive a national vaccination card that is used to record all immunizations, and basic medical and wellness evaluations from 0 to 9 years of age. Since July 2023, the national vaccination card includes and must have recorded the results of the five different screenings that are performed in newborns: metabolic, hearing, visual, cardiac, and hip dysplasia. Although ENBS is now mandated in Mexico, the number and list of conditions are unspecified and variable depending on the healthcare institution of parents' affiliation.

In Mexico, SMA screening remains unavailable in the national public healthcare system (and even limited in the private sector). Consequently, disease detection relies heavily on clinical expertise, which varies significantly within the country's medical community. Despite the absence of screening for the disease and the high cost of therapies, a few patients have been able to be treated in selected reference medical centers. The first patient treated in Mexico's public system with onasemnogene abeparvovec was infused at the Children's Hospital in Mexico City (*Hospital Infantil de México Federico Gómez*) at 10 months of age.

However, this delay in diagnosis and treatment for SMA sadly resulted in the patient dying from respiratory complications a couple of months later.

THE FUTURE AND EQUITY OF NEWBORN SCREENING

The development and implementation of next-generation genomic sequencing for the study of genetic disorders and, later on, for molecular clinical diagnostics of patients with rare genetic disorders has raised the possibility of utilizing genomic sequencing as a newborn screening tool. The utilization of modern genomic sequencing technologies offers the possibility to identify actionable genetic diseases promptly before symptom onset and beyond the limitations of identifying abnormal metabolites through MS/MS in ENBS. In the last few years, several pilot programs have been implemented to evaluate the feasibility, effectiveness, and impact of genomic newborn screening (gNBS) in sick and healthy newborns primarily in the United States and the United Kingdom[16-19]. Currently, at least thirty different gNBS programs are being planned or implemented on a research basis or commercially in Europe, the US, the UK, China, and Australia[20,21]. Issues regarding how many and which conditions to include, data analysis and variant interpretation, return of results, data privacy and storage, and data revisiting and custody are among the main themes that are being explored and discussed for gNBS programs[19-21]. While promising to improve the lives of millions of newborns in the corresponding countries, the current landscape of gNBS programs further reflects the disparities in the implementation of genomic sequencing for precision health around the world. The lack of representation of non-European ancestry individuals in genomic projects and databases is now a well-recognized problem, yet slow progress has been made in expanding genomic sequencing efforts to underrepresented populations[22]. A particular issue related to this is the interpretation of genomic data and variants for individuals from underrepresented populations like those in LAC. Studies that have assessed the diagnostic efficacy of genomic sequencing in patients from different ancestries, have shown a higher proportion of variants of unknown significance and a reduction in diagnostic efficacy for patients from admixed populations such as Hispanics and African Americans in the US[23,24]. The implementation of population-level genomics programs, including gNBS, can help not only expand the characterization of human genomic variation, but also clarify the clinical significance of variants of unknown significance for individuals from underrepresented populations in both high-income (HIC) and low- and middle-income countries (LMICs).

The question is not anymore whether gNBS should be done because research programs exploring its feasibility are already being planned or implemented in several countries, but what the best practices for these programs should be, their advantages and limitations, and how to ensure the equitable implementation of genomic technologies to reduce and not broaden health disparities around the world[18,25]. While HICs are already implementing research gNBS pilot programs to assess their feasibility for public health, LMICs like Mexico and most other LAC countries are tracking behind on the implementation of genomic technologies for the research and diagnosis of genetic diseases, let alone exploring their implementation at the population level or in gNBS programs. This gap in implementation is multifactorial, but a major factor is the cost of local genomic sequencing in LMICs, which can be 3-5 times higher than in HICs due to high import fees and taxes plus distributor fees for instruments and reagents.

Mexico was the first country in LAC to initiate NBS eleven years after NBS was mandated and implemented in some states in the United States, while other LAC countries have not yet implemented basic NBS programs. Proof of concept for the need to implement ENBS in Mexico was published in 2000[26], yet more than two decades later, ENBS is not being performed for most newborns in the country. Are the countries in the LAC region going to maintain this trend and explore implementing gNBS a decade or more later than more advanced countries?

Mexico and other LAC countries should start considering now how to best implement effective and comprehensive ENBS programs for their populations and in their primarily socialized healthcare systems. At the same time, governments and health authorities across the region ought to begin considerations for the implementation of modern and future early disease detection technologies for population health. While the time for adoption and implementation of MS/MS technologies for ENBS may have passed for the countries of the region, it is now timely to explore the implementation of the next generation of ENBS programs through research pilot projects that can assess their effectiveness and feasibility. Ideally, gNBS should be complimentary to metabolic ENBS using MS/MS; however, in countries where ENBS does not exist as the standard of care for newborns nationwide, the strategic investment in technologies that can maximize the benefit for as many newborns, patients, and families as possible should be considered.

Not only will this have an impact on improved health and life expectancy outcomes for newborns at risk, but it has been proven that early detection of rare genetic diseases is cost-effective for healthcare systems and societies in the long term[27-30]. Additionally, the ability to know the prevalence of diseases in local populations and the number of patients with conditions for which there is an available treatment can enable better national public health planning, budgeting, and price negotiation with pharmaceutical companies for improved access to treatments and proper disease management. In healthcare systems marked by limited resources and challenging access to new therapeutics for rare diseases, early diagnoses and interventions become imperative. Patients treated at advanced stages of a disease are at greater risk of long-term complications and disability, which not only profoundly impacts the patients and their families, but also the already constrained healthcare budgets and systems in resource-limited countries such as Mexico and those in the LAC region.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and writing of the original manuscript: Gonzaga-Jauregui C, Moreno-Salgado R, Tovar-Casas J, Navarrete-Martínez JI

Provided insightful comments and revised the manuscript: Gonzaga-Jauregui C, Tovar-Casas J, Navarrete-Martínez JI

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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