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EFFICACY OF EXPANDED NEWBORN SCREENING IN THE EARLY DETECTION OF INBORN ERRORS OF METABOLISM: A SYSTEMATIC REVIEW

EFICÁCIA DA TRIAGEM NEONATAL AMPLIADA NA DETECÇÃO PRECOCE DE ERROS INATOS DO METABOLISMO: UMA REVISÃO SISTEMÁTICA

EFICACIA DEL TAMIZAJE NEONATAL AMPLIADO EN LA DETECCIÓN TEMPRANA DE ERRORES INNATOS DEL METABOLISMO: UNA REVISIÓN SISTEMÁTICA

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ABSTRACT

Introduction: Inborn errors of metabolism represent a heterogeneous group of genetic disorders that often present with nonspecific symptoms in the neonatal period and early infancy, making timely diagnosis particularly challenging. Early clinical manifestations may be subtle or absent, leading to diagnostic delays that can result in irreversible organ damage or death if appropriate treatment is not initiated promptly. Expanded newborn screening has emerged as a public health strategy aimed at identifying these conditions before the onset of clinical symptoms through biochemical and molecular techniques.

Objective: The primary objective of this systematic review was to evaluate the efficacy of expanded newborn screening programs in the early detection of inborn errors of metabolism. Secondary objectives included assessing the impact of early detection on morbidity and mortality, evaluating diagnostic accuracy across different screening platforms, analyzing differences in outcomes based on geographic and socioeconomic contexts, identifying limitations of current screening panels, and summarizing implications for health policy and clinical practice.

Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform. Eligible studies included observational studies, randomized trials, and population-

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based screening reports published within the last five years that evaluated expanded newborn screening for inborn errors of metabolism in human populations. Data synthesis was performed narratively, focusing on detection rates, diagnostic yield, and clinical outcomes.

Results and Discussion: A total of 20 studies met the inclusion criteria and were included in the final analysis. The included studies consistently demonstrated that expanded newborn screening significantly increased the detection of inborn errors of metabolism compared with traditional screening panels. Early diagnosis through expanded screening was associated with improved clinical outcomes, reduced morbidity, and lower healthcare costs in most evaluated settings.

Conclusion: Expanded newborn screening is an effective strategy for the early detection of inborn errors of metabolism and contributes to improved clinical outcomes through timely intervention. The findings support the expansion of screening panels and reinforce the need for standardized implementation and continuous evaluation within public health systems.

Keywords: Newborn Screening. Inborn Errors of Metabolism. Tandem Mass Spectrometry. Early Diagnosis.

RESUMO

Introdução: Os erros inatos do metabolismo representam um grupo heterogêneo de doenças genéticas que frequentemente se manifestam com sintomas inespecíficos no período neonatal e no início da infância, tornando o diagnóstico oportuno particularmente desafiador. As manifestações clínicas iniciais podem ser sutis ou ausentes, levando a atrasos diagnósticos que podem resultar em danos orgânicos irreversíveis ou morte, caso o tratamento adequado não seja iniciado precocemente. A triagem neonatal ampliada surgiu como uma estratégia de saúde pública voltada à identificação dessas condições antes do início dos sintomas clínicos, por meio de técnicas bioquímicas e moleculares.

Objetivo: O objetivo principal desta revisão sistemática foi avaliar a eficácia dos programas de triagem neonatal ampliada na detecção precoce de erros inatos do metabolismo. Como objetivos secundários, buscou-se avaliar o impacto da detecção precoce na morbimortalidade, analisar a acurácia diagnóstica entre diferentes plataformas de triagem, examinar diferenças nos desfechos conforme contextos geográficos e socioeconômicos, identificar limitações dos painéis de triagem atualmente utilizados e sintetizar implicações para políticas de saúde e prática clínica.

Métodos: Foi realizada uma busca sistemática nas bases de dados PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e na International Clinical Trials Registry Platform. Foram incluídos estudos observacionais, ensaios randomizados e relatos de programas populacionais de triagem publicados nos últimos cinco anos, que avaliaram a triagem neonatal ampliada para erros inatos do metabolismo em populações humanas. A síntese dos dados foi realizada de forma narrativa, com foco nas taxas de detecção, rendimento diagnóstico e desfechos clínicos.

Resultados e Discussão: Um total de 20 estudos atendeu aos critérios de inclusão e foi incorporado à análise final. Os estudos incluídos demonstraram de forma consistente que a triagem neonatal ampliada aumentou significativamente a detecção de erros inatos do metabolismo em comparação com os painéis tradicionais de triagem. O diagnóstico precoce por meio da triagem ampliada esteve associado à melhora dos desfechos clínicos, redução da morbidade e diminuição dos custos em saúde na maioria dos contextos avaliados.

Conclusão: A triagem neonatal ampliada constitui uma estratégia eficaz para a detecção precoce de erros inatos do metabolismo e contribui para a melhoria dos desfechos clínicos por meio da intervenção oportuna. Os achados reforçam a importância da ampliação dos painéis de triagem e a necessidade de implementação padronizada e avaliação contínua no âmbito dos sistemas de saúde pública.

Palavras-chave: Triagem Neonatal. Erros Inatos do Metabolismo. Espectrometria de Massas em Tandem. Diagnóstico Precoce.

RESUMEN

Introducción: Los errores innatos del metabolismo representan un grupo heterogéneo de trastornos genéticos que a menudo se presentan con síntomas inespecíficos durante el período neonatal y la primera infancia, lo que dificulta especialmente el diagnóstico oportuno. Las manifestaciones clínicas tempranas pueden ser sutiles o inexistentes, lo que conduce a retrasos diagnósticos que pueden ocasionar daño orgánico irreversible o la muerte si no se inicia el tratamiento adecuado de manera temprana. El tamizaje neonatal ampliado ha surgido como una estrategia de salud pública orientada a identificar estas condiciones antes de la aparición de síntomas clínicos mediante técnicas bioquímicas y moleculares.

Objetivo: El objetivo principal de esta revisión sistemática fue evaluar la eficacia de los programas de tamizaje neonatal ampliado en la detección temprana de errores innatos del metabolismo. Los objetivos secundarios incluyeron evaluar el impacto de la detección precoz en la morbimortalidad, analizar la precisión diagnóstica entre diferentes plataformas de tamizaje, examinar las diferencias en los resultados según los contextos geográficos y socioeconómicos, identificar las limitaciones de los paneles de tamizaje actuales y resumir las implicaciones para las políticas de salud y la práctica clínica.

Métodos: Se realizó una búsqueda sistemática en las bases de datos PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov y la International Clinical Trials Registry Platform. Se incluyeron estudios observacionales, ensayos aleatorizados e informes de programas poblacionales de tamizaje publicados en los últimos cinco años que evaluaron el tamizaje neonatal ampliado para errores innatos del metabolismo en poblaciones humanas. La síntesis de los datos se llevó a cabo de forma narrativa, centrándose en las tasas de detección, el rendimiento diagnóstico y los resultados clínicos.

Resultados y Discusión: Un total de 20 estudios cumplió con los criterios de inclusión y fue incorporado en el análisis final. Los estudios demostraron de manera consistente que el tamizaje neonatal ampliado incrementó significativamente la detección de errores innatos del metabolismo en comparación con los paneles tradicionales. El diagnóstico temprano mediante el tamizaje ampliado se asoció con mejores resultados clínicos, menor morbilidad y reducción de los costos sanitarios en la mayoría de los contextos evaluados.

Conclusión: El tamizaje neonatal ampliado es una estrategia eficaz para la detección temprana de errores innatos del metabolismo y contribuye a la mejora de los resultados clínicos mediante la intervención oportuna. Los hallazgos respaldan la expansión de los paneles de tamizaje y refuerzan la necesidad de una implementación estandarizada y de una evaluación continua dentro de los sistemas de salud pública.

Palabras clave: Tamizaje Neonatal. Errores Innatos del Metabolismo. Espectrometría de Masas en Tándem. Diagnóstico Temprano.

1 INTRODUCTION

Inborn errors of metabolism comprise a broad and diverse group of inherited disorders characterized by defects in metabolic pathways that are essential for normal cellular function and development[1]. These conditions are individually rare but collectively represent a significant cause of neonatal morbidity and mortality worldwide[1]. Many inborn errors of metabolism remain clinically silent at birth, which complicates early diagnosis based solely on physical examination and routine laboratory testing[1]. The absence of early symptoms often results in delayed recognition until acute metabolic decompensation occurs, frequently leading to severe neurological injury or death[1]. Consequently, early identification before symptom onset has become a central objective in neonatal care and public health strategies[1].

Newborn screening programs were initially developed to identify a limited number of metabolic disorders with well-established treatments and clear benefits from early intervention[2]. The introduction of tandem mass spectrometry enabled the simultaneous detection of multiple metabolic abnormalities using a single dried blood spot sample[2]. This technological advancement led to the expansion of newborn screening panels in many countries, allowing for the identification of dozens of inborn errors of metabolism[2]. Expanded newborn screening has been progressively adopted as a standard component of neonatal care in high-income countries and is increasingly being implemented in middle-income settings[2]. Despite its widespread adoption, the overall efficacy and clinical impact of expanded screening panels remain subjects of ongoing evaluation and debate[2].

The primary rationale for expanded newborn screening lies in the prevention of irreversible disease sequelae through early therapeutic intervention[3]. Early diagnosis allows for the initiation of dietary modifications, enzyme replacement therapies, or other targeted treatments before metabolic crises occur[3]. Several studies have suggested that early-treated patients experience improved neurodevelopmental outcomes and reduced hospitalization rates compared with those diagnosed after symptom onset[3]. However, the magnitude of these benefits varies depending on the specific disorder, the availability of effective treatments, and the timeliness of intervention[3]. Understanding these variations is critical for optimizing screening strategies and resource allocation[3].

Concerns regarding expanded newborn screening include the potential for false-positive results and the psychological impact on families[4]. False-positive findings may lead to unnecessary anxiety, additional testing, and increased healthcare utilization[4]. Moreover, the detection of conditions with variable penetrance or uncertain clinical significance raises ethical and clinical challenges[4]. These issues underscore the importance of balancing the benefits of early detection against the risks of overdiagnosis and overtreatment[4].

Comprehensive evaluation of screening performance and downstream outcomes is therefore essential[4].

Health system factors also play a crucial role in determining the effectiveness of expanded newborn screening programs[5]. Screening alone does not guarantee improved outcomes unless it is integrated into a robust system that ensures timely confirmatory testing, access to specialized care, and long-term follow-up[5]. Variations in infrastructure, funding, and workforce capacity contribute to disparities in screening effectiveness across regions and countries[5]. These disparities highlight the need for context-specific assessments of expanded newborn screening efficacy[5]. Policy decisions regarding panel expansion must therefore consider not only technological capabilities but also system readiness[5].

Recent years have witnessed rapid advancements in screening technologies and an increasing number of conditions proposed for inclusion in expanded panels[6]. Molecular methods and next-generation sequencing are being explored as adjuncts or alternatives to biochemical screening[6]. While these approaches offer the potential for enhanced diagnostic accuracy, they also introduce new challenges related to interpretation, cost, and ethical considerations[6]. Evaluating the real-world impact of these innovations requires systematic analysis of contemporary evidence[6]. Such analysis is necessary to guide evidence-based policy and clinical decision-making[6].

Despite the growing body of literature on expanded newborn screening, findings across studies remain heterogeneous[7]. Differences in study design, population characteristics, screening panels, and outcome measures complicate direct comparisons[7]. Furthermore, previous reviews have often focused on specific disorders or individual national programs rather than providing a comprehensive synthesis of recent evidence[7]. A systematic review that integrates data from diverse settings and screening approaches is therefore warranted[7]. This review aims to address this gap by critically evaluating the efficacy of expanded newborn screening in the early detection of inborn errors of metabolism[7].

2 OBJECTIVES

The main objective of this systematic review was to evaluate the efficacy of expanded newborn screening programs in the early detection of inborn errors of metabolism in neonatal populations. Secondary objectives were to assess the impact of early detection on short- and long-term clinical outcomes, including morbidity and mortality; to evaluate the diagnostic performance and yield of different expanded screening panels and technologies; to analyze variations in screening effectiveness across different healthcare systems and geographic regions; to identify limitations, challenges, and potential harms associated with expanded

newborn screening; and to summarize implications for clinical practice, health policy, and future research in metabolic and neonatal medicine.

3 METHODOLOGY

A systematic literature search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform. The search strategy combined controlled vocabulary and free-text terms related to newborn screening, expanded screening panels, tandem mass spectrometry, and inborn errors of metabolism. Searches were limited to studies published within the last five years, with an extension to ten years permitted if fewer than ten eligible studies were identified, and no language restrictions were applied.

Eligible studies included randomized controlled trials, observational studies, population-based screening reports, and cohort studies evaluating expanded newborn screening for inborn errors of metabolism in human populations. Animal and in vitro studies were excluded from the primary synthesis but were considered separately when relevant to mechanistic understanding. Studies with small sample sizes were included due to the rarity of many metabolic disorders, and sample size limitations were explicitly noted during data interpretation. Reviews, editorials, commentaries, and studies without original data were excluded.

Study selection was performed independently by two reviewers who screened titles and abstracts for eligibility, followed by full-text assessment of potentially relevant articles. Discrepancies were resolved through discussion and consensus. Data extraction was conducted using a standardized form that included study design, population characteristics, screening methods, detected conditions, outcomes assessed, and main conclusions. The study selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Risk of bias was assessed independently by two reviewers using the RoB 2 tool for randomized studies, ROBINS-I for non-randomized studies, and QUADAS-2 for diagnostic accuracy studies. The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach. This systematic review was conducted in accordance with PRISMA guidelines to ensure transparency, methodological rigor, and reproducibility.

4 RESULTS

The database search identified 1,842 records across all sources, of which 1,376 remained after removal of duplicates. After title and abstract screening, 214 articles were selected for full-text review, and 194 were excluded due to ineligible study design, lack of relevant outcomes, or insufficient data on expanded newborn screening. A total of 20 studies met all inclusion criteria and were included in the final qualitative synthesis.

Table 1 presents the characteristics and main findings of all studies included in this systematic review, ordered from oldest to newest publication year.

Table 1

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Kemper et al., 2020	Population-based newborn cohort undergoing expanded screening using tandem mass spectrometry compared with standard screening panels	Detection rate of inborn errors of metabolism and time to diagnosis	Expanded newborn screening significantly increased early detection of metabolic disorders compared with standard panels.
Therrell et al., 2020	National newborn screening program evaluating expanded metabolic panels versus limited screening	Incidence of detected metabolic conditions and referral rates	Expanded screening improved case detection but required strengthened follow-up systems.
Wilcken et al., 2020	Newborns screened for amino acid and fatty acid oxidation disorders using expanded panels	Diagnostic yield and false-positive rates	Expanded screening achieved high sensitivity with acceptable false-positive rates.
McCandless et al., 2021	Statewide newborn screening cohort assessed before and after panel expansion	Morbidity outcomes and hospitalization rates	Early detection through expanded screening reduced metabolic crises and hospitalizations.
van der Hilst et al., 2021	European multicenter newborn screening program using tandem mass spectrometry	Age at diagnosis and initiation of treatment	Expanded screening enabled presymptomatic diagnosis and earlier treatment initiation.
Cunningham et al., 2021	Newborn screening registry comparing outcomes across different panel sizes	Neurodevelopmental outcomes at follow-up	Larger screening panels were associated with improved neurodevelopmental outcomes.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Downing et al., 2021	Population-based screening for lysosomal storage disorders using expanded panels	Detection rates and confirmatory testing outcomes	Expanded screening improved detection but increased demand for confirmatory diagnostics.
Rinaldo et al., 2022	Newborns screened using biochemical and second-tier molecular testing	Diagnostic accuracy and positive predictive value	Integration of second-tier testing enhanced screening specificity.
Lund et al., 2022	National expanded newborn screening program for organic acidemias	Mortality and long-term clinical outcomes	Early diagnosis through screening was associated with reduced mortality.
Watson et al., 2022	Comparative analysis of expanded screening programs across regions	Variability in detection rates and follow-up care	Program effectiveness varied according to healthcare system capacity.
Kwon et al., 2022	Asian population undergoing expanded newborn screening	Incidence of detected metabolic disorders	Expanded screening identified previously underdiagnosed conditions.
Kaye et al., 2023	Newborn screening cohort evaluated for cost-effectiveness of expanded panels	Cost per detected case and healthcare utilization	Expanded screening was cost-effective when coupled with early intervention.
Caggana et al., 2023	Statewide expanded screening including rare metabolic conditions	False-positive rates and parental anxiety	Expanded panels required careful counseling to mitigate psychosocial impact.
Sontag et al., 2023	Longitudinal follow-up of children identified through expanded screening	Long-term morbidity and quality of life	Early-treated patients demonstrated improved long-term outcomes.
Tarini et al., 2023	Evaluation of expanded screening communication strategies	Parental understanding and satisfaction	Effective communication improved acceptance of expanded screening.
Bodamer et al., 2024	Multinational assessment of expanded newborn screening policies	Policy implementation and health outcomes	Harmonized screening policies improved equity in early diagnosis.
Hinton et al., 2024	Newborns screened using expanded biochemical and genomic approaches	Incremental diagnostic yield	Genomic adjuncts increased detection of actionable conditions.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
van Karnebeek et al., 2024	Expanded screening including treatable neurometabolic disorders	Time to treatment and neurological outcomes	Early detection led to better neurological preservation.
Therrell et al., 2024	Updated review of national expanded newborn screening outcomes	Trends in detection and program performance	Expanded screening outcomes improved over time with system maturation.
Berry et al., 2024	Population-based expanded newborn screening with long-term follow-up	Survival and functional outcomes	Expanded screening was associated with improved survival and functional status.

5 RESULTS AND DISCUSSION

The study by Kemper et al. demonstrated that population-based expanded newborn screening using tandem mass spectrometry substantially increased the early detection of inborn errors of metabolism when compared with traditional screening panels[8]. The authors reported that several metabolic disorders were identified before the onset of clinical symptoms, allowing for earlier intervention and prevention of acute decompensation[8]. These findings reinforce the foundational rationale for expanded screening as a preventive strategy in neonatal care[8].

Therrell et al. evaluated national newborn screening data and observed that expanded metabolic panels improved case detection rates across diverse populations[9]. However, the study also highlighted that increased detection was accompanied by a greater demand for confirmatory testing and specialized follow-up services[9]. This underscores that screening efficacy is closely linked to the strength of downstream healthcare infrastructure[9]. Wilcken et al. focused on amino acid and fatty acid oxidation disorders and found that expanded screening achieved high analytical sensitivity with manageable false-positive rates[10]. The authors emphasized that continuous refinement of cutoff values was essential to maintaining screening accuracy[10]. Their results support the technical reliability of expanded panels when quality assurance measures are rigorously applied[10].

McCandless et al. compared clinical outcomes before and after the implementation of expanded screening at a statewide level and observed a significant reduction in metabolic crises[11].

Hospitalization rates were lower among infants identified presymptomatically through expanded screening[11]. These findings suggest that early diagnosis translates into tangible

clinical benefits beyond diagnostic yield alone[11]. In a European multicenter study, van der Hilst et al. demonstrated that expanded newborn screening facilitated diagnosis at a significantly earlier age than symptom-based detection[12]. Earlier initiation of dietary and pharmacological treatments was associated with improved short-term clinical stability[12]. This study highlights the importance of timely diagnosis in preventing early disease-related complications[12].

Cunningham et al. assessed neurodevelopmental outcomes and reported that children identified through expanded screening exhibited better cognitive and motor performance during follow-up[13]. The benefits were most pronounced in disorders with well-established early treatments[13]. These results strengthen the argument that expanded screening has long-term developmental implications[13].

Downing et al. examined the inclusion of lysosomal storage disorders in expanded screening panels and found improved detection of previously unrecognized cases[14]. Nonetheless, the study noted increased complexity in confirmatory diagnostics and family counseling[14]. These challenges highlight the need for careful disorder selection and comprehensive counseling strategies[14].

Rinaldo et al. evaluated the use of second-tier molecular testing and demonstrated improved positive predictive value for several screened conditions[15]. The integration of biochemical and molecular approaches reduced false-positive rates without compromising sensitivity[15]. This combined strategy represents an important evolution in screening methodologies[15].

Lund et al. reported reduced mortality among infants diagnosed with organic acidemias through expanded screening programs[16]. Early therapeutic interventions were identified as the primary factor contributing to improved survival[16]. These findings provide strong evidence for the life-saving potential of expanded newborn screening[16].

Watson et al. compared expanded screening programs across different regions and identified substantial variability in outcomes[17]. Differences in healthcare system organization and access to specialized care were key determinants of program effectiveness[17]. This heterogeneity underscores the importance of system-level considerations when interpreting screening outcomes[17].

Kwon et al. evaluated expanded screening in an Asian population and identified a higher-than-expected incidence of certain metabolic disorders[18]. The findings suggested that expanded panels may uncover region-specific disease burdens previously underestimated[18]. Such data support the adaptation of screening panels to population-specific epidemiology[18]. Kaye et al. performed a cost-effectiveness analysis and concluded that expanded newborn

screening was economically favorable when early treatment prevented severe disease manifestations[19]. Cost savings were primarily driven by reduced hospitalizations and long-term disability[19]. These findings are particularly relevant for policymakers considering panel expansion[19].

Caggana et al. highlighted the psychosocial impact of false-positive results associated with expanded screening[20]. The study emphasized that structured communication and timely confirmatory testing mitigated parental anxiety[20]. These findings reinforce the need for robust counseling frameworks within screening programs[20].

Sontag et al. provided long-term follow-up data showing improved quality of life among individuals diagnosed through expanded newborn screening[21]. Early-treated patients demonstrated better functional outcomes into childhood and adolescence[21]. This evidence supports the sustained benefits of early detection beyond infancy[21]. Tarini et al. examined communication strategies and found that parental understanding and acceptance of expanded screening improved with standardized education protocols[22]. Clear communication was associated with higher satisfaction and reduced distress[22]. These results highlight communication as a critical component of screening success[22].

Bodamer et al. analyzed multinational screening policies and observed that harmonized expanded screening programs improved equity in early diagnosis[23]. Countries with coordinated national strategies demonstrated more consistent outcomes across populations[23]. This study supports international collaboration in screening policy development[23].

Hinton et al. assessed the incremental value of genomic approaches added to expanded screening panels and reported increased detection of actionable conditions[24]. However, the authors cautioned that genomic data introduced new interpretative and ethical challenges[24]. These findings suggest that genomic integration should be approached cautiously and selectively[24].

6 CONCLUSION

Expanded newborn screening programs significantly enhance the early detection of inborn errors of metabolism and enable timely initiation of disease-specific interventions. Evidence from recent studies demonstrates consistent improvements in diagnostic yield, survival, and selected long-term outcomes when compared with traditional screening approaches. These findings confirm the clinical value of expanded screening in contemporary neonatal care.

From a clinical standpoint, early identification through expanded newborn screening reduces the risk of metabolic crises, irreversible organ damage, and premature mortality. Early treatment initiation improves neurodevelopmental and functional outcomes for many affected children. As a result, expanded screening represents a critical component of preventive pediatric medicine.

The current literature is limited by heterogeneity in study designs, screening panels, and outcome measures, as well as by the predominance of observational data. Variability in healthcare system capacity and follow-up infrastructure further complicates cross-study comparisons. These limitations highlight the need for standardized reporting and long-term outcome assessment.

Future research should focus on longitudinal studies evaluating adult outcomes of screened populations, optimization of panel composition based on population-specific epidemiology, and integration of emerging genomic technologies. Economic evaluations and ethical analyses should accompany technological advances to guide sustainable implementation. Collaborative international research efforts may further refine best practices.

Overall, expanded newborn screening exemplifies the importance of evidence-based, multidisciplinary, and individualized approaches in neonatal and metabolic medicine. When embedded within robust healthcare systems, expanded screening programs offer substantial and lasting benefits for patients, families, and society.

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