

ADVANCING NEWBORN SCREENING IN SPAIN: A CONSENSUS-BASED PROPOSAL FOR A UNIFORM PANEL

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ON BEHALF OF THE NEONATAL SCREENING STUDY GROUP OF AECOM⁴



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ABSTRACT – Objective: Newborn screening (NBS) is a vital public health initiative that enables early detection of congenital disorders. Spain currently lacks a standardized national panel, leading to regional disparities in the conditions screened. Therefore, the aim of this study is to present the development and proposed implementation of the Spanish Uniform Screening Panel (SUSP), a standardized national newborn screening framework designed to harmonize screening practices across Spain.

Materials and Methods: This manuscript presents the Spanish Uniform Screening Panel (SUSP), developed through a nationwide consensus by all metabolic screening centers in Spain and Portugal. The panel is based on biomarkers currently in use and distinguishes between primary and secondary conditions. The methodology includes a review of existing biomarkers, classification criteria, and a proposal for a national advisory process.

Results: The panel comprises 85 conditions, including 41 primary and 44 secondary conditions, supported by standardized nomenclature and ORPHA codes. Diseases without current pilot data or operational biomarkers were excluded, but are discussed with a pathway for future inclusion. A roadmap is also proposed for genomic NBS integration.

Conclusions: The Spanish Uniform Screening Panel (SUSP) represents a milestone in the national newborn screening strategy. Through a collaborative consensus process involving all regional screening centers and based on real-world biomarker usage, this proposal addresses long-standing disparities. It lays the groundwork for equitable, evidence-based screening across Spain. This harmonized approach ensures consistency, facilitates national reporting and evaluation, and strengthens Spain's capacity to adapt to future technological advances.

KEYWORDS: Newborn screening, SUSP, Metabolic disease, Congenital disease.

INTRODUCTION

Newborn screening (NBS) programs are designed to detect conditions that, if untreated, can lead to significant morbidity, mortality, or disability. Early diagnosis facilitates timely interventions, dramatically improving health outcomes. Spain boasts considerable strengths in the screening, diagnosis, and follow-up of inborn errors of metabolism (IEMs). These strengths stem from pioneering efforts in neonatal screening since the 1960s and the adoption of technologies, such as tandem mass spectrometry (MS/MS), which

have significantly expanded diagnostic capacity and accuracy¹. Furthermore, Spain has established a collaborative network of specialized centers and healthcare professionals, enabling the delivery of high-quality care and monitoring for rare diseases². However, while the USA has established the Recommended Uniform Screening Panel (RUSP) as a standardized model³, and Italy has enacted a national law that makes neonatal screening mandatory nationwide – with a decree defining the panel of conditions included in the Extended Neonatal Screening (ENS) program^{4,5} – Spain’s NBS program remains fragmented, with significant regional variations in the conditions covered and the terminology used.

In Spain, each autonomous community defines its own NBS program, leading to discrepancies in the disorders screened and the terminology used. Key issues include:

- Inconsistent nomenclature: Variations in naming and classifying conditions complicate data sharing and collaboration across regions⁶.
- Unequal coverage: Some regions include only primary conditions, while others incorporate secondary conditions, leading to disparities in early diagnosis and treatment⁴.
- Lack of central oversight: There is no unified body to standardize criteria for the inclusion of conditions or to evaluate emerging technologies and treatments⁵.
- Risk of political influence: Regional variation in the number of conditions included may lead to political manipulation, prioritizing quantity over quality and equity of services.

The European landscape is equally diverse, with International Society for Neonatal Screening (ISNS) and European Commission (EC) reports⁷ highlighting a clear need for harmonization. This lack of uniformity results in inequities in health access and outcomes, underscoring the urgent need for a harmonized approach.

MATERIALS AND METHODS

Proposed Framework for the Spanish Uniform Screening Panel (SUSP)

The SUSP is the result of a structured consensus reached by all newborn screening centers in Spain and Portugal under the coordination of the Neonatal Screening Working Group of AECOM.

This process was grounded in current clinical practice and laboratory capabilities. The starting point was the set of conditions that had already been screened in participating metabolic laboratories. For each condition, we verified that at least one specific biomarker, already implemented in routine practice, was available. Each condition was then reviewed and classified as either primary, if it is the direct target of a specific biomarker, or secondary, if it is identified incidentally through differential diagnosis during screening for a primary condition. Only pathologies detectable with biomarkers currently in use across national labs were considered.

The inclusion criteria were applied uniformly across centers, aligning with established principles for screening programs, such as those outlined by Wilson and Jungner⁸, which emphasize the public health relevance of the condition, the availability of effective treatment, and the feasibility of early detection. In addition to these core criteria, we also considered the current diagnostic capacity of national laboratories to ensure operational feasibility. Thus, the final selection reflects both scientific criteria and the practical implementation context across Spain.

This transparent and collaborative approach ensures that the panel is grounded in feasibility and aligned with shared clinical priorities.

To maintain the panel’s integrity and ensure its scientific and technical validity, the inclusion of new diseases must be overseen by a national advisory board. This multidisciplinary board should evaluate proposals based on feasibility, clinical benefit, and the existence of pilot data demonstrating real-world performance. New biomarkers or screening strategies will not be included unless prior evidence from validated pilots in Spanish laboratories is available.

Criteria for Inclusion

Conditions will be evaluated based on the following:

- Net health benefit: Evidence that screening improves outcomes through early diagnosis and intervention⁹.
- Technical feasibility: Availability of reliable and validated screening methods⁶.
- Treatment accessibility: Existence of effective treatments or interventions to mitigate disease impact⁵.

Primary and Secondary Conditions

Similar to the RUSP, the SUSP will distinguish between:

- Primary conditions: Disorders for which screening directly identifies affected newborns³.
- Secondary conditions: Disorders detected as part of the differential diagnosis of a core condition⁹.

Standardized Nomenclature

A unified terminology will align with international standards, facilitating collaboration and epidemiological research. Italy's ENS has successfully implemented such a standardization, proving its feasibility and benefits^{4,5}.

RESULTS

Based on the RUSP³, ENS^{4,5}, and the epidemiological context in Spain, a total of 85 conditions were included based on expert consensus: 41 classified as primary and 44 as secondary. The full list, including associated ORPHAcodes, is provided in [Appendix 1](#).

Implementation Strategy

Key steps for the implementation of the Spanish Uniform Screening Panel include the formation of a national advisory board, centralization of data registries, harmonized nomenclature, and ongoing review mechanisms.

1. *Surveys and Consensus Building*

The final list of conditions in the SUSP was determined through a rigorous national consensus process coordinated by the Neonatal Screening Study Group of AECOM. All metabolic screening centers in Spain and Portugal participated in this process, which included structured surveys, expert workshops, and iterative rounds of review.

Comprehensive surveys were conducted across all newborn screening centers in Spain to gather insights on current practices, challenges, and priorities. The feedback was used to build Consensus on the proposed SUSP. The consensus proposal has been submitted to the Ministry of Health, with the objective of normalizing the screening offerings across autonomous communities¹⁰.

2. *Establishment of a National Committee*

A multidisciplinary committee, including clinicians, researchers, and policymakers, will oversee the SUSP, evaluate emerging evidence, and recommend updates⁵.

3. *Screening Procedure Standardization*

National guidelines will ensure consistent methodologies and technologies for screening across regions.

4. *National Registry Platform*

To ensure comprehensive data collection and monitoring, a national platform for registering all newborn screening cases should be established. This registry will serve as a central repository for data, enabling analysis of program effectiveness, tracking of outcomes, and facilitating research collaborations. It will also lay the groundwork for incorporating future genomic technologies into the screening process.

5. *Funding and Resources Allocation*

The Spanish government must allocate resources to support implementation, including laboratory infrastructure, training, and public awareness campaigns⁵.

6. *Monitoring and Evaluation*

Data collection and analysis will enable continuous quality improvement and guide future updates to the panel.

DISCUSSION

This structured model, while inspired by the U.S. RUSP and the Italian ENS, reflects Spain's specific infrastructure and capabilities. As in Italy, where national legislation is supported by scientific review and regional readiness, Spain's model reinforces quality and feasibility over quantity. This is particularly relevant in the context of emerging multiplex technologies, such as enzymatic assays for lysosomal storage disorders, which may identify additional secondary conditions and require dynamic panel updates.

Consideration of Additional Disorders Not Currently Included

Disorders such as mucopolysaccharidosis (MPS) II, Krabbe disease, Leber's congenital amaurosis, and other conditions lacking pilot validation were not included in the current version of the SUSP. Future consideration will require feasibility studies, validation in national laboratories, and advisory board review before potential inclusion.

Future Directions: Genomic NBS

The emergence of genomic NBS signifies a major transition from traditional models reliant on metabolic or enzymatic biomarkers. While the current SUSP distinguishes between primary and secondary conditions based on the biomarker used, this distinction becomes less relevant in a genomic framework.

In genomic NBS, decision-making shifts from identifying measurable biomarkers to selecting pathogenic variants for analysis based on factors such as disease burden, severity, age of onset, and the availability of treatment or early intervention. This model requires a predefined set of actionable genes and variants curated through national Consensus and reviewed by a multidisciplinary advisory board. Variant interpretation must be standardized, and analysis should be limited to conditions where early detection offers clear health benefits and ethical acceptability.

In this future model, biomarkers will no longer determine inclusion in the panel; rather, they may serve as confirmatory or secondary diagnostic tools. The genomic-first approach emphasizes proactive decision-making: what is analyzed must be determined before sequencing takes place, in accordance with public health goals, technical capabilities, and social acceptability.

Spain must prepare for this transition through pilot studies, ethical guidelines, professional training, and the development of an official genomic NBS strategy that is aligned with European and global standards.

CONCLUSIONS

The creation of the SUSP marks a crucial step in the national harmonization of NBS. Developed through consensus and rooted in technical feasibility, this panel ensures equitable access and provides a scalable model for future innovation and adaptation.

The inclusion of a national registry and preparation for genomic screening further positions Spain at the forefront of neonatal health innovation. Crucially, the framework prioritizes quality and equity, ensuring that the number of conditions included does not become a tool for political advantage but rather serves the best interests of all newborns across the country. Spain's leadership in MS/MS implementation and its expertise in rare metabolic diseases uniquely position it to lead the European effort in expanding and harmonizing newborn screening programs. The proposed Spanish Uniform Screening Panel will ensure equitable access to life-saving interventions, fostering a healthier start for all newborns in Spain.

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Artificial Intelligence was not used for this study and for the preparation of the manuscript.

AUTHORS' CONTRIBUTIONS:

Judith García-Villoria, Carmen Delgado-Pecellín, Rosa M. López and Domingo González-Lamuño conceived and designed the study (conceptualization, methodology, supervision), as well as wrote and reviewed the paper.

The following individuals, listed in alphabetical order, are co-authors and members of the Neonatal Screening Study Group of AECOM who have contributed to the consensus and signed this manuscript: Aguilar Castillo, María José; Álvarez Ríos, Ana Isabel; Anadón Ruiz, Aránzazu Isabel; Argudo Ramírez, Ana; Bauçà Rosselló, Josep Miquel; Bóveda Fontán, María Dolores; Bueno Llarena, María Josefa; Cañadas Garzó, Verónica; Castiñeiras Ramos, Daisy; Cocho de Juan, José Ángel; Colón Mejeras, Cristóbal;

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CONFLICT OF INTEREST:

The authors declare no conflicts of interest.

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Not applicable.

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