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Review

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Development of newborn screening policies in Spain 2003-2022: what do we actually need to reach an agreement?

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Abstract

Newborn screening (NBS) for inherited disorders is recognized as an essential public health intervention to improve health outcomes in the newborn population. The implementation of an NBS programme requires an evaluation of effectiveness, safety, cost-effectiveness, feasibility, and budget impact. Determining which of the known disorders should be included in NBS programmes is a public health policy challenge. In this context, economic evaluation aims to contribute to the sustainability of public health systems, but the appropriate economic evaluation framework for these interventions is still unclear. Existing NBS programmes vary widely in the number and type of disorders screened, even among the most developed European countries, despite the fact that the core criteria for guiding policy decision-making are standard. In Spain, where delivery of NBS programmes is marked by heterogeneity between regions, guidelines based on the best available scientific evidence are being established in order to achieve standardization of NBS policies and programmes at a national level. This paper

provides a general overview of existing evidence-based health-policy initiatives aimed at enhancing the equity and efficiency of the NBS programme in Spain and their impact on health decisions. We also describe existing challenges to reduce uncertainty, and the variations observed in decisions relating to the content and procedures used in NBS programmes.

Keywords: Newborn screening, inherited disorders, health-policy, equity

INCREASING INEQUALITIES IN NEWBORN SCREENING IN THE EUROPEAN UNION

NBS for inherited disorders is recognized as an essential public health intervention to improve health outcomes in the newborn population, by identifying and treating infants with life-threatening or debilitating disorders early in post-natal life, before clinical symptoms appear[1,2]. Determining which of the known disorders should be included in NBS programmes is a public health policy challenge that must take into account different perspectives (e.g., medicine, science, public policy, advocacy, ethics, and economics)[3]. The scientific evidence available to support decisions about which conditions should be included in NBS is often quantitatively and qualitatively limited, making it difficult to anticipate expected long-term outcomes that may occur, in order to support decision-making about extending NBS[4,5]. Policy makers and stakeholders must often rely on incomplete data and limited scientific evidence to decide whether a rapid expansion of the NBS panel is more desirable than maintaining a more deliberative pace[6,7]. Existing NBS programmes vary widely in the number and type of disorders screened[8-10], even among the most developed European countries, despite the fact that the core criteria for guiding policy decision-making are standard[11,12]. These criteria not only include an assessment of the effectiveness of the NBS but stress the need to assess economic consequences alongside other factors such as acceptance[11-13]. These policy variations and their consequences, such as health inequalities from the earlier stages of life, occur internationally and intra-nationally, regardless of epidemiological and socio-economic issues[14], especially in European countries such as Spain with decentralized governmental jurisdictions.

Past technological advances allowed for the expansion of NBS services[15-20], due mainly to the proven favourable performance and low costs of tandem mass spectrometry (MS/MS)[21,22], the development of new therapeutic options (e.g., gene therapy and enzyme replacement therapies), and improved knowledge of some inherited metabolic disorders[8,23]. Moreover, differences in the application and interpretation of universal screening implementation criteria at a health-policy level are increasing the variations observed in the contents of NBS programmes[9]. It is likely that with the increasing potential of next-generation genomic sequencing in NBS, these differences may become even more pronounced in the coming years[14], despite relevant uncertainties linked to classic Wilson and Jungner criteria, such as lack of knowledge about the natural history of many screened diseases, the potential harm of false-positive screening tests, the limited availability of effective treatments, or economic, social and ethical considerations[24]. Regardless of the existing frameworks for guiding health policy screening decisions[25], the subjective character of some criteria, such as the importance of the health problem in question, together with the accessibility of new, effective, and cost-effective screening methods, variations in the interpretation of available evidence for a given condition, and the public advocacy by families, professionals, and state legislators, have led to some of the observed variations[14].

Economic data relating to NBS have often been based on cost estimates rather than complete economic evaluations and opportunity-cost considerations[26,27]. Costs have played a favourable role in decisions because the direct costs of additional screening tests are relatively low, regardless of the considerable uncertainty about the effectiveness of available treatment options[26-29]. The role of costs needs to be

considered in depth and early on in the decision-making process. This is due to variations in treatment costs, hospital-billing policy, the requisite infrastructure (at all stages) and personnel cost of running the programme, as well as additional expertise and follow-up systems for surveillance. All of these aspects will affect the viability and sustainability of the NBS programme[6,30-33]. Aside from costs, additional unexplored variations in value judgments, driven by technological availability, social or professional pressure, or political opportunity, usually not explicitly stated, could play a differential role in policy decision-making[34].

There is no evidence to show that those populations who receive NBS for fewer disorders, such as in the UK, France, several Spanish regions, and Finland, are at a higher risk of poorer health outcomes than the populations of Austria, Italy, or Iceland, where NBS programmes cover more than 25 different conditions[3]. Moreover, governments are committed to ensuring the value of all health care provided to the population, as well as the long-term sustainability of the health care system per se. This commitment has recently been exacerbated by the double impact of the 2008 economic and financial crisis and the direct and collateral pandemic effects of COVID-19[35].

EVIDENCE-BASED HEALTH POLICY INITIATIVES TO ENHANCE EQUITY AND EFFICIENCY FOR THE NBS PROGRAMME IN SPAIN

The Spanish National Health Service (SNHS) is a decentralized public health insurance system with universal coverage, which provides free health care to every resident in all of the country's Autonomous Regions (ARs). The SNHS is managed at a regional level and fully financed by national insurance contributions and taxes, though some regional governments allocate local budgets to provide additional funding. The national government established three health policy instruments to support the decentralization of health planning and management competencies in each ARs: (1) the Spanish General Health Care Act, guaranteeing free and universal healthcare access to all Spanish residents[36]; (2) the National Benefits Catalogue to ensure equity in the supply of healthcare services[37]; (3) the Inter-territorial Board of the SNHS (made up of central and regional public health authorities). However, even though these health-policy instruments were established early to ensure equity, homogeneity, and efficiency in a decentralized SNHS, variations have since occurred in the supply of healthcare services, including NBS programmes[26].

Universal NBS, introduced in 1968 in Spain, is a well-established programme funded by every AR. It is currently organized through a network of 20 regional laboratories with an overall coverage of over 98% of the neonatal population. By 2000, the AR of Galicia had implemented a pioneering expanded NBS programme based on MS/MS for more than 40 conditions[23], at a time when the country's remaining ARs were mainly screening for phenylketonuria (PKU) and hypothyroidism. Despite the fact that the Galician programme was not expressly developed as a research initiative, it has nonetheless generated new knowledge about the true prevalence of a wide spectrum of disorders and relationships between biomarkers and disease expression in that region of Spain[38]. Subsequently, the SNHS Cohesion and Quality was operationalized by means of Quality Plans supported by the Spanish Network for Health Technology Assessment (RedETS), with the aim of bolstering evidence-based health policies and limiting variations in the supply of healthcare services among ARs[39]. As a result, there has been a growing demand for evidence and justification of value in the context of innovation and health technology assessment (HTA), whether to endorse funding, coverage, and reimbursement decisions or, alternatively, to support price negotiations[40].

To standardize the offer of NBS and reduce inequalities in the SNHS, the Spanish Ministry of Health prompted the creation of (1) a Framework Document to guide NBS decisions approved by the Public Health Commission of the SNHS Inter-territorial Board; (2) an expert group to develop recommendations on (i) a uniform screening panel; (ii) minimal standards for NBS in all ARs;

(iii) a decision matrix for potential NBS expansion; (iv) a common quality-assurance process; (v) the development of a common information system for assessment, linked to the NBS. This expert group received scientific and technical support from RedETS through a series of HTA reports commissioned by the expert group, pursuant to an iterative consultative process involving national experts and AR health authorities. HTA reports delivered by RedETS provide appraised, evidence-based information on the safety, effectiveness, cost-effectiveness, legal, ethical, organizational, and environmental aspects of all non-pharmaceutical technologies[41].

COST-EFFECTIVENESS ISSUES IN NBS AND ITS DEVELOPMENT IN SPAIN

As previously reported, NBS cost estimates may be underestimated due to the relative inexpensiveness of adding "just one more test" to an existing screening panel. However, the cumulative cost of screening is beyond the test cost itself, in that it increases with the necessary acquisition of testing equipment, materials, plant, and staff[33]. According to the Hasting Reports[30], a health policy decision-making framework for NBS should be based on scientific evidence, in addition to (1) taking overall opportunity costs into account; (2) distributing the cost and benefits of the programme fairly; (3) respecting human rights[24]. Beyond cost estimates of the potential incorporation of new disorders into NBS programmes, the need for cost-effectiveness analysis (CEA) results in the decision-making process is justified because the costs and health outcomes per screened newborn (comprising follow-up testing and subsequent lifelong treatment) are extended to all newborns at regional or national levels.

In 2012, Langer *et al.* drew up specific guidelines to assess and improve the methodological quality of economic evaluations of NBS. The authors assessed 12 CEA studies on NBS for inherited metabolic disorders by MS/MS, reporting differences in cost categories considered (from both health services and societal perspectives)[42]. When adopting the health services perspective, the costs should include those pertaining to the NBS programme as well as treatment and follow-up. The societal perspective should consider, in addition, the lost productivity of patients and informal caregivers[42]. Furthermore, one of the main problems confronting economic evaluations of NBS relates to the lack of epidemiological data and health outcomes (in terms of morbidity and mortality)[42]. In 2020, a scoping review on the challenges of economic evaluations of NBS showed that the methodological quality of these types of studies continues to be irregular[27].

In an economic evaluation, effectiveness is preferably measured by means of quality-adjusted life years (QALYs) gained. A QALY measures the health state of a person or group by adjusting the length of life to reflect the quality of life. The QALYs provide a common measure to compare the benefits gained from different alternative interventions. The threshold of willingness to pay for an additional QALY in Spain has been estimated at around €25,000/QALY[43]. However, the low frequency of these disorders and the methodological complexities of estimating QALYs justify the fact that life years (LY) gained are used as an alternative outcome measure[42,44].

The validity and robustness of CEA estimates are limited by the uncertainty of relevant parameters (incidence of disorders, short-term screening effectiveness, and the long-term consequences of screening). Addressing this uncertainty requires the use of simulation modelling techniques[42,44] and corresponding sensitivity analyses that depend on arguable assumptions. Logistic and ethical considerations lead to the absence of clinical trials on NBS, making it necessary to use effectiveness data from case series, mainly short-term, very small, and subject to biases. Well-structured and completed population-based registries, which include the necessary long-term follow-up of cases as well as comprehensive information on the natural history of diseases, would seem a promising tool to improve the availability and validity of data.

NBS's impact on health service utilization and health outcomes might be lifelong. However, the effect of screening on early identification of conditions is mainly based on extrapolated short-term outcomes and data quantification in adulthood is inadequate. Consequently, CEAs are restricted to short timeframes based on the available information or, alternatively, incorporate an appropriate time horizon relying on assumptions. Specific aspects such as incidence, prevalence and costs are likely to be different between countries, not only for NBS itself, but also for all subsequent treatment and follow-up activities. Therefore, the transferability to different contexts of CEAs on NBS is limited and requires review, revision, and adaptation on the basis of local data[44].

Since 2006, an HTA perspective, including CEA, has been required by the Spanish Ministry of Health for decision-making on the potential extension of the national NBS programme (available from[39]). Unfortunately, as epidemiological, clinical, and economic data relating to NBS are in short supply and unreliable, CEA studies are limited. From 2006 to 2022, RedETS provided evidence of the effectiveness and cost-effectiveness of an expanded NBS programme at the national level. RedETS drew up CEAs comparing costs and outcomes for 16 different disorders from both societal and national health system perspectives. The first CEA report carried out in 2006 determined the cost-effectiveness of MS/MS to screen PKU and medium chain 3-hydroxyacyl-CoA dehydrogenase deficiency (MCADD) in Spain, with an incremental cost-effectiveness ratio (ICER) below €6000/LY[22]. Following this report, RedETS estimated the ICER of adding five new disorders to the NBS national programme (based on MS/MS for PKU and MCADD): homocystinuria, long chain 3-hydroxyacyl- CoA dehydrogenase deficiency (LCHADD), maple syrup urine disease, isovaleric acidaemia and glutaric aciduria type 1 (GA-I)[44]. The incorporation of this set of diseases yielded an ICER of €28,000/LY approximately. Subsequently, other reports were prepared in which the cost-effectiveness of neonatal screening for different diseases, not all of which subject to MS/MS, was estimated: sickle cell disease, cystic fibrosis, biotinidase deficiency, congenital adrenal hyperplasia, galactosaemia, methylmalonic and propionic acidaemia, tyrosinaemia type I, primary carnitine deficiency (CUD), very long-chain acyl-CoA dehydrogenase deficiency (VLCAD), and severe combined immunodeficiency (SCID) (available from[39]). It should be noted that the results of these reports showed that adding propionic and methylmalonic acidaemia, VLCAD, and CUD to the national NBS programme is a cost-effective alternative in Spain (ICER: €21,405/QALY, €10,723/LY and €14,217/LY, respectively). In sharp contrast, the ICER for tyrosinaemia type 1 was €30,034/QALY. In addition, other diseases whose screening was shown to be a cost-effective technology were biotinidase, congenital adrenal hyperplasia, or cystic fibrosis (all of them yielded ICERs of below €30,000/LY). Finally, sickle cell disease screening would be cost-effective if the cost per newborn screened did not exceed €2.5 and SCID screening would be below the Spanish cost-effectiveness threshold of €25,000 per QALY[43] as long as the cost of the screening test does not exceed €4 per newborn[39].

From the evidence generated in this set of HTA reports, a set of seven disorders were included in the national NBS programme in 2014 (hypothyroidism, PKU, cystic fibrosis, sickle cell disease, MCADD, LCHADD, and GA-I[44]) and four additional diseases were added in 2022 (biotinidase deficiency, maple syrup urine disease, homocystinuria, and congenital adrenal hyperplasia[39]). The Spanish NBS programme could be expanded in the near future, depending upon new scientific evidence, the development of new detection biomarkers, enhanced knowledge of the natural history, and new therapies that may possibly emerge for the respective disorders.

STAKEHOLDER PARTICIPATION TO SUPPORT DECISION-MAKING ON NEWBORN SCREENING IN SPAIN

Beyond cost-effectiveness, several other previously mentioned factors influence policy-making in NBS. Differences in the interpretation and management of uncertainties in these factors might explain observed

variations in the content of NBS programmes at a regional/national level[16,45]. Moreover, as the number of disorders added to NBS programmes increases, maintaining a balance between privacy and the rights of society (parents), a debate arises as to the use of screening in cases where the reliability and availability of treatment are limited. Hence, to explore the "benefit potentials" of screening, RedETS involved patient associations, expert physicians, scientific societies, and public health professionals along the HTA process, in order to inform policy decisions.

The relatives of affected people, integrated into officially constituted patient associations, were deliberately involved from the beginning of the evaluation process of each of the selected disorders so that they could make their viewpoint known and make a contribution to relevant aspects[46-48]. In addition, a call to participate was made to the major patient federations that bring together most patient associations, such as the Patient Platform, the Spanish Patient Forum, the Spanish Federation of Rare Diseases, and the Spanish Federation of Metabolic Diseases. Designated representatives were included as collaborating experts in the teams that laid the foundations for drawing up both the protocol and the assessment report.

Scientific societies linked either to the technology to be assessed or to the health problem targeted, such as the Spanish Association for the Study of Inborn Errors of Metabolism (AECOM), Spanish Paediatrics Association (AEP), Spanish Society of Inborn Errors of Metabolism (SEEIM), Spanish Society of Laboratory Medicine, Perinatal Diagnosis Commission (SEQCML-DP), Spanish Society of Epidemiology (SEE), Rare Diseases Research Institute (IIER), and the Federation of Spanish Medical Scientific Associations, were also invited to take part as experts in the drafting of HTA reports. Additionally, individual experts were sought through an informal review of indexed scientific publications related to the subject, and invited to participate in the preparation of the report. Similarly, industry representatives were invited to participate in the assessment process from its inception, undertake protocol data verification and provide additional information of interest. In the end, they were able to review the final report and make amendments to it.

IMPACT OF EVIDENCE-BASED HEALTH POLICY DECISION-MAKING FOR NBS IN SPAIN

Table 1 shows changes in the number of neonatal disorders included in regional NBS programmes in Spain between 2003 and 2020. As can be seen, there was an increase in regional variations, despite the SNHS Inter-territorial Board's recommendations to the ARs, made by the experts and based on the availability of a wide series of HTA reports issued by RedETS. Although a group of six ARs accepted the Ministry of Health's recommendations, offering evidence-based NBS programmes limited to seven disorders of proven effectiveness and cost-effectiveness, other ARs offer programmes in which the number of screened disorders ranges from 18 to 40.

WHAT WE HAVE LEARNT

As shown, the Spanish Ministry of Health considers evidence-based data essential to inform decisions on NBS programme revisions. Therefore, considering the natural history and consequences of a given disorder, the accuracy of screening for it, the harms and benefits of early diagnosis[2], and the opportunity cost of publicly funding it are key elements in the decision-making process[39,44]. Unfortunately, in Spain and other countries, common NBS programme policy decisions are often made with limited evidence and incomplete data. Decisions around these public health programmes become challenging when disorders are rare with a low incidence, advocates have a stronger role in decisions, new treatments are emerging, and technology makes NBS more feasible[49], sometimes with undesirable results[50].

Table 1. Number of neonatal disorders included in regional NBS programmes: Spain 2003 and 2020

Spain	2003* Without availability of HTA reports	2020 Supported by HTA reports
Castilla-León	3	7
Asturias	3	7
Baleares	3	7
Canarias	2	7
Cantabria	2	7
Navarra	2	7
Valencia	3	7
Pais Vasco	2	7
Extremadura	5	18
Madrid	3	18
Castilla La Mancha	4	22
Cataluña	3	25
Aragón	3	30
La Rioja	3	30
Galicia	25	30
Andalucía	3	35
Murcia	3	40

*Data should be taken with caution, given the lack of validated records from 2003.

This paper shows that variations in the content of NBS programmes can actually increase, notwithstanding the existence of a specific procedure to guide decisions based on the critical evaluation of the best available scientific evidence of such programmes' effectiveness, cost-effectiveness, and economic, organizational, ethical, and social impacts. Although the data reported here refer to different Spanish regions, similar findings are observed in other developed countries worldwide[10,51]. It is possible that some of the differences observed among countries could be accounted for by the different considerations of economic aspects in general, and, particularly, the availability and consideration of economic evaluations adapted to each country[10,52]. While in some cases, there is no information available on the cost-effectiveness of the screening programmes under consideration, in others, this information is not valued or used, regardless of whether it might be available[53,54]. It is somewhat more difficult to interpret the differences observed between the Spanish ARs, which seem to fall into two blocs, one that clearly adheres to recommendations based on cost-effectiveness criteria, and the other, in which application of this criterion might be diluted by the effect of other potential considerations.

Economic evaluation, in terms of cost-effectiveness or cost-utility, is a central component of health technology assessment reports to inform public funding decisions for new interventions, given that budgets do not grow at the speed at which healthcare innovations of potential value do. Precisely to ensure that available budgets are allocated to fund innovations of the greatest value to health, CEAs combine costs and health outcomes and compare them with those corresponding to other innovations, possibly even outside the scope of NBS programmes. This procedure brings transparency and reproducibility to decision-making. It is true, however, that this procedure might stop funding emerging for diagnostic or therapeutic innovations aimed at people affected by rare diseases, for which there are few alternatives, either because of the relative lack of robust evidence of their efficacy or their high cost. In order to address the barrier posed by the cost of innovations in the field of rare diseases, without sacrificing transparency and reproducibility in decision-making, one proposal is to establish threshold values of willingness to pay other than those of the general population[55,56]. Another procedure increasingly used to guide innovation-funding decisions

uses Multicriteria Decision Analysis to ensure that all relevant criteria, including societal values, are considered in a more open and participatory manner, in which costs or cost-effectiveness data do not constitute a limiting barrier[57,58].

In this scenario of searching for procedures to inform health policy decisions in a manner that is responsible, transparent, reproducible, participatory, and sensitive to the unmet needs of society, it is still necessary to intensify efforts to obtain more valid information on effectiveness by making available information on relevant health outcomes. Sharing research information and promoting pilot studies among international partners is a vital part of the process of expanding NBS, by developing consistent case definitions for conditions included within NBS programmes, helping to ensure the interoperability of long-term outcome studies to increase the availability of screening, and subsequently benefiting wider populations[24]. Opportunity costs and potential benefits beyond the child should be factored in, thus structuring a policy that will distribute costs and benefits fairly[30].

Regional studies using long-term observational designs have been set in motion in some countries to evaluate the feasibility, diagnostic-process quality, and population distribution of biomarkers, by defining cut-off values, establishing patient-care pathways and algorithms for patient care, and measuring longer-term relevant health benefits[58-60]. Furthermore, national registries for inborn errors of metabolism have been implemented to assess outcomes at a population level, while also acting as electronic medical records that help clinicians monitor treatment and record progress, as in Sweden[61]. To address substantial gaps in NBS evidence, the US State of North Carolina established the Early Check initiative as a translational research enterprise embedded in a public health programme, with the dual aim of informing NBS policy and quantifying the potential benefits and risks of early identification and pre-symptomatic treatment of infants that have rare disorders, for a select number of conditions, offered as a supplement to standard NBS to all birthing parents under a voluntary research protocol[2]. Similarly, the Spanish Ministry of Health has developed Post-Launch Evidence Generation (PLEG) studies, which can provide post-marketing real-world evidence, thereby enlarging the scope of HTA in the life cycle of innovations[62] while making the innovation under research accessible to society. The PLEG studies can be boosted at the request of health authorities, because of their need to rely on additional evidence to make decisions about innovations with high potential value but limited knowledge regarding their long-term effects. Despite the interest in these regional/national initiatives, as the COVID-19 pandemic has recently revealed, more international collaboration within the European Union is required to increase sample sizes and reduce the uncertainty of the different parameters of NBS programmes, something that translates as substantial variations in the number of disorders screened and, probably, in the quality of their application and the results obtained in the short, medium, and long term.

It is possible, however, that all these efforts to reduce uncertainty and variations in decisions relating to the content and procedures used in NBS programmes would not suffice to resolve the inequalities in the supply of services between territories, as shown in this paper. It is also necessary to know and understand both the decision-making processes and the criteria applied by the decision-makers in the different Spanish regions, which have resulted in such different decisions, after starting from agreed political principles and a set of common data based on scientific evidence. Accordingly, qualitative research must be incorporated into these aspects, covering all the actors involved in decision-making.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study, performed data interpretation, revised the draft critically for important intellectual content and finally approved the version to be

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Performed data acquisition and interpretation, as well as providing technical and material support and revising the draft critically: Renata Linertová R, Guirado-Fuentes C, Hernández-Yumar A, Paz-Valiñas L, Cantero-Muñoz P

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REFERENCES
1. Bailey DB Jr. A window of opportunity for newborn screening. *Mol Diagn Ther* 2022;26:253-61. DOI PubMed PMC
2. Bailey DB Jr, Gehtland LM, Lewis MA, et al. Early check: translational science at the intersection of public health and newborn screening. *BMC Pediatr* 2019;19:238. DOI PubMed PMC
3. Loeber JG, Burgard P, Cornel MC, et al. Newborn screening programmes in Europe; arguments and efforts regarding harmonization. Part 1. From blood spot to screening result. *J Inherit Metab Dis* 2012;35:603-11. DOI PubMed
4. Chan K, Brower A, Williams MS. Population-based screening of newborns: Findings from the newborn screening expansion study (part two). *Front Genet* 2022;13:867354. DOI PubMed PMC
5. Kemper AR, Green NS, Calonge N, et al. Decision-making process for conditions nominated to the recommended uniform screening panel: statement of the US Department of Health and Human Services Secretary's Advisory Committee on heritable disorders in newborns and children. *Genet Med* 2014;16:183-7. DOI
6. Brower A, Chan K, Williams M, et al. Population-based screening of newborns: findings from the NBS expansion study (part one). *Front Genet* 2022;13:867337. DOI PubMed PMC
7. Lyon J. Concerns over newborn screening. *JAMA* 2017;317:576. DOI PubMed
8. Jones SA, Cheillan D, Chakrapani A, et al. Application of a novel algorithm for expanding newborn screening for inherited metabolic disorders across Europe. *Int J Neonatal Screen* 2022;8:20. DOI PubMed PMC
9. Loeber JG, Platis D, Zetterström RH, et al. Neonatal screening in Europe revisited: an ISNS perspective on the current state and developments since 2010. *Int J Neonatal Screen* 2021;7:15. DOI
10. Scarpa M, Bonham JR, Dionisi-Vici C, et al. Newborn screening as a fully integrated system to stimulate equity in neonatal screening in Europe. *Lancet Reg Health Eur* 2022;13:100311. DOI PubMed PMC
11. Wilson JMG, Jungner G; World Health Organization. principles and practice of screening for disease. Geneva; 1968. Available from: https://niercheck.nl/wp-content/uploads/2019/06/Wilson-Jungner-1968.pdf [Last accessed on 13 Sep 2023]
12. Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ* 2008;86:317-9. DOI PubMed PMC
13. Jansen ME, Metternick-Jones SC, Lister KJ. International differences in the evaluation of conditions for newborn bloodspot screening: a review of scientific literature and policy documents. *Eur J Hum Genet* 2016;25:10-6. DOI PubMed PMC
14. Sikonja J, Groselj U, Scarpa M, et al. Towards achieving equity and innovation in newborn screening across Europe. *Int J Neonatal Screen* 2022;8:31. DOI PubMed PMC
15. Botkin JR, Clayton EW, Fost NC, et al. Newborn screening technology: proceed with caution. *Pediatrics* 2006;117:1793-9. DOI
16. Friedman JM, Cornel MC, Goldenberg AJ, Lister KJ, Sénécal K, Vears DF; Global Alliance for Genomics and Health Regulatory and Ethics Working Group Paediatric Task Team. Genomic newborn screening: public health policy considerations and recommendations.

BMC Med Genomics 2017;10:9. DOI PubMed PMC

17. Howard HC, Knoppers BM, Cornel MC, Wright Clayton E, Sénécal K, Borry P; European Society of Human Genetics; P3G International Paediatric Platform; Human Genome Organisation; and the PHG Foundation. Whole-genome sequencing in newborn screening? A statement on the continued importance of targeted approaches in newborn screening programmes. *Eur J Hum Genet* 2015;23:1593-600. DOI PubMed PMC
18. Johnston J, Lantos JD, Goldenberg A, Chen F, Parens E, Koenig BA; members of the NSIGHT Ethics and Policy Advisory Board. Sequencing newborns: a call for nuanced use of genomic technologies. *Hastings Cent Rep* 2018;48 Suppl 2:S2-6. DOI PubMed PMC
19. Knoppers BM, Sénécal K, Borry P, Avard D. Whole-genome sequencing in newborn screening programs. *Sci Transl Med* 2014;6:229cm2. DOI PubMed
20. Potter BK, Avard D, Entwistle V, et al. Ethical, legal, and social issues in health technology assessment for prenatal/preconceptional and newborn screening: a workshop report. *Public Health Genomics* 2009;12:4-10. DOI PubMed PMC
21. Castilla I, Arvelo-Martín A, Valcárcel-Nazco C, et al. Cost-effectiveness of the expanded newborn screening of congenital errors of metabolism using tandem mass spectrometry. Available from: https://sescs.es/coste-efectividad-cribado-de-errores-congenitos-del-metabolismo-mediante-espectrometria-de-masas/ [Last accessed on 13 Sep 2023]
22. Ramos-Goñi JM, Serrano-Aguilar PG, Espada Sáenz-Torres M, Posada de la Paz M. Coste-efectividad del cribado neonatal de los errores congénitos del metabolismo mediante espectrometría de masas en tándem. Madrid; 2008. Report No.: Servicio de Evaluación del Servicio Canario de la Salud. SESCS; 2006. Available from: https://sescs.es/coste-efectividad-del-cribado-neonatal-por-espectrometria-de-masas-en-tandem/ [Last accessed on 13 Sep 2023]
23. Castiñeras DE, Couce ML, Marin JL, González-Lamuño D, Rocha H. Newborn screening for metabolic disorders in Spain and worldwide. *An Pediatr* 2019;91:128.e1-14. DOI PubMed
24. Chan K, Petros M. Simple test, complex system: multifaceted views of newborn screening science, technology, and policy. *Glob Pediatr Health* 2019;6:2333794X19894812. DOI PubMed PMC
25. Hoffmann GF, Lindner M, Loeber JG. 50 years of newborn screening. *J Inherit Metab Dis* 2014;37:163-4. DOI PubMed
26. Serrano-aguilar P, Castilla-rodríguez I, Vallejo-torres L, Valcárcel-nazco C, García-pérez L. Neonatal screening in Spain and cost-effectiveness. *Expert Opinion on Orphan Drugs* 2015;3:971-4. DOI
27. Cacciatore P, Visser LA, Buyukkaramikli N, van der Ploeg CPB, van den Akker-van Marle ME. The methodological quality and challenges in conducting economic evaluations of newborn screening: a scoping review. *Int J Neonatal Screen* 2020;6:94. DOI PubMed PMC
28. Garavito GA, Moniz T, Déom N, Redin F, Pichini A, Vindrola-Padros C. The implementation of large-scale genomic screening or diagnostic programmes: A rapid evidence review. *Eur J Hum Genet* 2023;31:282-95. DOI PubMed PMC
29. Pollitt RJ, Green A, Mccabe CJ, et al. Neonatal screening for inborn errors of metabolism: cost, yield and outcome: a review. *Health Technol Asses* 1997:1. DOI
30. Baily MA, Murray TH. Ethics, evidence, and cost in newborn screening. *Hastings Cent Rep* 2008;38:23-31. DOI
31. Chan K, Davis J, Pai SY, Bonilla FA, Puck JM, Apkon M. A markov model to analyze cost-effectiveness of screening for severe combined immunodeficiency (SCID). *Mol Genet Metab* 2011;104:383-9. DOI PubMed PMC
32. Gaspar HB, Hammarström L, Mahlaoui N, Borte M, Borte S. The case for mandatory newborn screening for severe combined immunodeficiency (SCID). *J Clin Immunol* 2014;34:393-7. DOI PubMed
33. Johnson K, Lloyd-Puryear MA, Mann MY, Ramos LR, Therrell BL. Financing state newborn screening programs: sources and uses of funds. *Pediatrics* 2006;117:S270-9. DOI PubMed
34. Howell RR. Ethical issues surrounding newborn screening. *Int J Neonatal Screen* 2021;7:3. DOI PubMed PMC
35. Simon D, Broadbridge E, Baker M, et al. Common challenges and identified solutions for state newborn screening programs during COVID-19 pandemic. *Int J Neonatal Screen* 2022;8:7. DOI PubMed PMC
36. Ley 14/1986, de 25 de abril, General de Sanidad. Available from: https://www.boe.es/eli/es/l/1986/04/25/14/con [Last accessed on 9 Sep 2023].
37. Royal Decree 1030/2006, of September 15, which establishes the portfolio of common services of the National Health System and the procedure for updating it. Available from: https://www.boe.es/eli/es/rd/2006/09/15/1030/con [Last accessed on 13 Sep 2023].
38. Couce ML, Castiñeiras DE, Bóveda MD, et al. Evaluation and long-term follow-up of infants with inborn errors of metabolism identified in an expanded screening programme. *Mol Genet Metab* 2011;104:470-5. DOI
39. The Spanish Network of Agencies for Health Technology Assessment and Services of the National Health System (RedETS); 2023. Available from: https://redets.sanidad.gob.es/ [Last accessed on 9 Sep 2023].
40. Royal Decree-Law 16/2012, of April 20, on urgent measures to guarantee the sustainability of the National Health System and improve the quality and safety of its benefits; 2012. Available from: https://www.boe.es/eli/es/rdl/2012/04/20/16/con [Last accessed on 9 Sep 2023].
41. Sobrido Prieto M, González Guitián C, Cerdá Mota T, group of technicians and experts in documentation, and diffusion/dissemination belonging to the Spanish Health Technology Assessment Agencies & Units. Strategies for the diffusion and dissemination of health technology assessment (HTA) products. Madrid: Ministry of Science & Innovation; 2010. Available from: https://redets.sanidad.gob.es/productos/buscarProductos.do?metodo=descargarFichero&idProducto=135 [Last accessed on 9 Sep 2023].
42. Langer A, Holle R, John J. Specific guidelines for assessing and improving the methodological quality of economic evaluations of newborn screening. *BMC Health Serv Res* 2012;12:300. DOI PubMed PMC

43. Vallejo-Torres L, García-Lorenzo B, Serrano-Aguilar P. Estimating a cost-effectiveness threshold for the Spanish NHS. *Health Econ* 2018;27:746-61. DOI PubMed
44. Valcárcel-Nazco C, García-Pérez L, Linertová R, et al. Cost-effectiveness methods of newborn screening assessment. *Rev Esp Salud Publica* 2021;95:e202101009. Available from: https://www.mscbs.gob.es/biblioPublic/publicaciones/recursos_propios/resp/revista_cdrom/VOL95/C_ESPECIALES/RS95C_202101009.pdf [Last accessed on 9 Sep 2023]
45. Grosse SD, Thompson JD, Ding Y, Glass M. The use of economic evaluation to inform newborn screening policy decisions: the washington state experience. *Milbank Q* 2016;94:366-91. DOI PubMed PMC
46. Forman J, Coyle F, Levy-Fisch J, Roberts P, Terry S, Legge M. Screening criteria: the need to deal with new developments and ethical issues in newborn metabolic screening. *J Community Genet* 2013;4:59-67. DOI PubMed PMC
47. Nicholls SG, Southern KW. Informed choice for newborn blood spot screening in the United Kingdom: a survey of parental perceptions. *Pediatrics* 2012;130:e1527-33. DOI PubMed
48. Wright SJ, Ulph F, Dharni N, Payne K. Eliciting preferences for information provision in newborn bloodspot screening programs. *Value Health* 2017;20:651-61. DOI PubMed
49. Bailey DB Jr, Gehtland L. Newborn screening: evolving challenges in an era of rapid discovery. *JAMA* 2015;313:1511-2. DOI PubMed PMC
50. Wasserstein MP, Andriola M, Arnold G, et al. Clinical outcomes of children with abnormal newborn screening results for Krabbe disease in New York State. *Genet Med* 2016;18:1235-43. DOI
51. Howson CP, Cedergren B, Giugliani R, et al. Universal newborn screening: a roadmap for action. *Mol Genet Metab* 2018;124:177-83. DOI
52. Pollitt RJ. International perspectives on newborn screening. *J Inherit Metab Dis* 2006;29:390-6. DOI PubMed
53. Fischer KE, Grosse SD, Rogowski WH. The role of health technology assessment in coverage decisions on newborn screening. *Int J Technol Assess Health Care* 2011;27:313-21. DOI PubMed
54. Fischer KE, Rogowski WH. Funding decisions for newborn screening: a comparative review of 22 decision processes in Europe. *Int J Environ Res Public Health* 2014;11:5403-30. DOI PubMed PMC
55. Cameron D, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Glob Health Action* 2018;11:1447828. DOI PubMed PMC
56. Eichler HG, Kong SX, Gerth WC, Mavros P, Jönsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? *Value Health* 2004;7:518-28. DOI PubMed
57. Marsh KD, Sculpher M, Caro JJ, Tervonen T. The use of MCDA in HTA: great potential, but more effort needed. *Value Health* 2018;21:394-7. DOI PubMed
58. Boy N, Mengler K, Thimm E, et al. Newborn screening: a disease-changing intervention for glutaric aciduria type 1. *Ann Neurol* 2018;83:970-9. DOI
59. Gramer G, Fang-Hoffmann J, Feyh P, et al. Newborn screening for vitamin B12 deficiency in Germany-strategies, results, and public health implications. *J Pediatr* 2020;216:165-72.e4. DOI
60. Mütze U, Garbade SF, Gramer G, et al. Long-term outcomes of individuals with metabolic diseases identified through newborn screening. *Pediatrics* 2020;146:e20200444. DOI
61. Hall K. 12th ISNS European regional meeting oral and poster abstracts. *Int J Neonatal Screen* 2021;7:71. DOI PubMed PMC
62. Garrison LP Jr, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health* 2007;10:326-35. DOI PubMed