Cost-Effectiveness Analysis of a National Newborn Screening Program for Biotinidase Deficiency

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abstract

BACKGROUND AND OBJECTIVES: There are conflicting views as to whether testing for biotinidase deficiency (BD) ought to be incorporated into universal newborn screening (NBS) programs. The aim of this study was to evaluate the cost-effectiveness of adding BD to the panel of conditions currently screened under the national NBS program in Spain.

METHODS: We used information from the regional NBS program for BD that has been in place in the Spanish region of Galicia since 1987. These data, along with other sources, were used to develop a cost-effectiveness decision model that compared lifetime costs and health outcomes of a national birth cohort of newborns with and without an early detection program. The analysis took the perspective of the Spanish National Health Service. Effectiveness was measured in terms of quality-adjusted life years (QALYs). We undertook extensive sensitivity analyses around the main model assumptions, including a probabilistic sensitivity analysis.

RESULTS: In the base case analysis, NBS for BD led to higher QALYs and higher health care costs, with an estimated incremental cost per QALY gained of $24 677. Lower costs per QALY gained were found when conservative assumptions were relaxed, yielding cost savings in some scenarios. The probability that BD screening was cost-effective was estimated to be >70% in the base case at a standard threshold value.

CONCLUSIONS: This study indicates that NBS for BD is likely to be a cost-effective use of resources.

WHAT'S KNOWN ON THIS SUBJECT: Biotinidase deficiency (BD) might cause severe and permanent consequences. Cases detected through newborn screening and under treatment are shown to remain asymptomatic. However, some countries, including Spain, do not provide universal BD screening within their national newborn screening programs.

WHAT THIS STUDY ADDS: It provides a first estimate of the lifetime costs and health outcomes of a Spanish birth cohort with and without neonatal screening for BD. It shows that newborn screening for BD is likely to be a cost-effective use of resources.

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Biotin, a water-soluble B complex vitamin, is the coenzyme for 4 carboxylases in humans that are essential for gluconeogenesis, fatty acid synthesis, and the catabolism of several branched-chain amino acids.[1–3] Biotinidase deficiency (BD) is an autosomal recessive inherited disorder in which the enzyme, biotinidase, is defective and the vitamin, biotin, is not recycled.[4] This disorder can be categorized as profound BD (<10% of mean normal activity in serum) and partial BD (10%–30% of normal activity). A study including 14 countries and 8 million screened babies between 1984 and 1990[5] estimated a worldwide incidence of 1 in 60 000 for combined cases, 1 in 112 271 for profound BD, and 1 in 129 282 for partial BD.

If untreated, people with BD might develop neurologic and cutaneous symptoms, including seizures, hypotonia, skin rash, alopecia, ataxia, cognitive deficits, optic atrophy, and sensorineural hearing loss. Some children might manifest only a single feature, whereas others exhibit a full spectrum of findings.[1,3,4,6] Most children with untreated profound deficiency experience the clinical symptoms of BD. Children with partial BD may exhibit any of the aforementioned features, but usually the symptoms are milder and occur only under metabolic stress.[2]

Treatment of BD consists of lifelong supplementation with oral biotin, although there is some controversy as to whether partial BD cases ought to receive this treatment.[2] Several studies have shown that early detected cases under treatment remain asymptomatic.[6–13] Cases detected after the onset of clinical symptoms improve after treatment with biotin, but some features are irreversible.

Universal screening in newborns for BD is available in ~25 countries worldwide.[14] However, some countries do not recommend universal BD testing. For instance, in the United Kingdom the National Screening Committee recommended that systematic population screening for BD should not be offered. One of the key issues informing this decision was the lack of evidence about the cost-effectiveness of neonatal BD screening.[15]

In Spain, only 2 regions (Galicia, since 1987, and Murcia, since 2007) include BD in their regional newborn screening (NBS) programs. Currently, the Spanish Ministry of Health, Social Services and Equality (MSSSI, in Spanish) is working to harmonize the NBS programs that are offered in different regions of Spain, where the panel of screened diseases can range from 2 to 27 disorders. The selection of the diseases to be included in the national screening panel is based on a series of requirements, which include cost-effectiveness considerations. The aim of this study is to evaluate the cost-effectiveness of adding BD to the national NBS program in Spain.

METHODS

Overview

Cost-effectiveness analysis provides a framework to compare competing health care alternatives in terms of health outcomes and costs and provides a useful tool for decision-making under budget constraints. In this analysis we simulate and compare the lifetime costs and health outcomes of a Spanish birth cohort with and without an NBS program for BD.

The analysis took the perspective of the National Health Service (NHS). In a separate analysis we also considered costs related to the "system for autonomy and care of dependent persons," because those are incurred under the payer's budget, that is, the MSSSI. Effectiveness was measured in terms of quality-adjusted life years (QALYs). QALYs are a measure of health-related quality of life (QoL) that combines information on QoL and length of life and is widely recommended in economic evaluations.[16] Costs were calculated in 2013€ and expressed in US$2013 with an implied conversion factor of €1 = US$1.36, based on the purchasing power parity ratio between Spain and the United States in 2013.[17]

The cost-effectiveness analysis was based on a decision analytical model. The model took the form of a decision tree, shown in a simplified form in Fig 1. Under the screening strategy, for which we assume 100% coverage, the screening test can yield a positive or negative result, with all positive tests prompting a second test. After 2 positive screening results, a newborn will undergo diagnostic tests. These tests could confirm that the newborn is affected by BD (true-positive) and therefore will start treatment to manage the condition, or the test could be negative (false-positive), indicating that the newborn is not affected by BD. In principle it is possible to observe false-negatives (ie, BD cases that showed negative screening results). In these cases, and for all BD cases under the nonscreening strategy, patients will follow the natural history of the disease with a series of possible outcomes.

Cost-effectiveness was summarized as the incremental cost-effectiveness ratio (ICER), defined as the incremental cost divided by the incremental effectiveness of 2 competing alternatives.[18] The ICER represents the additional cost needed to achieve 1 additional unit of effectiveness. The ICER is then compared with the decision makers' willingness-to-pay threshold to draw conclusions about the cost-effectiveness of the intervention. In Spain there is not an explicit threshold, but a reference value of €30 000 per QALY[19] has been estimated (~$40 000 per QALY). The time horizon of the analysis was

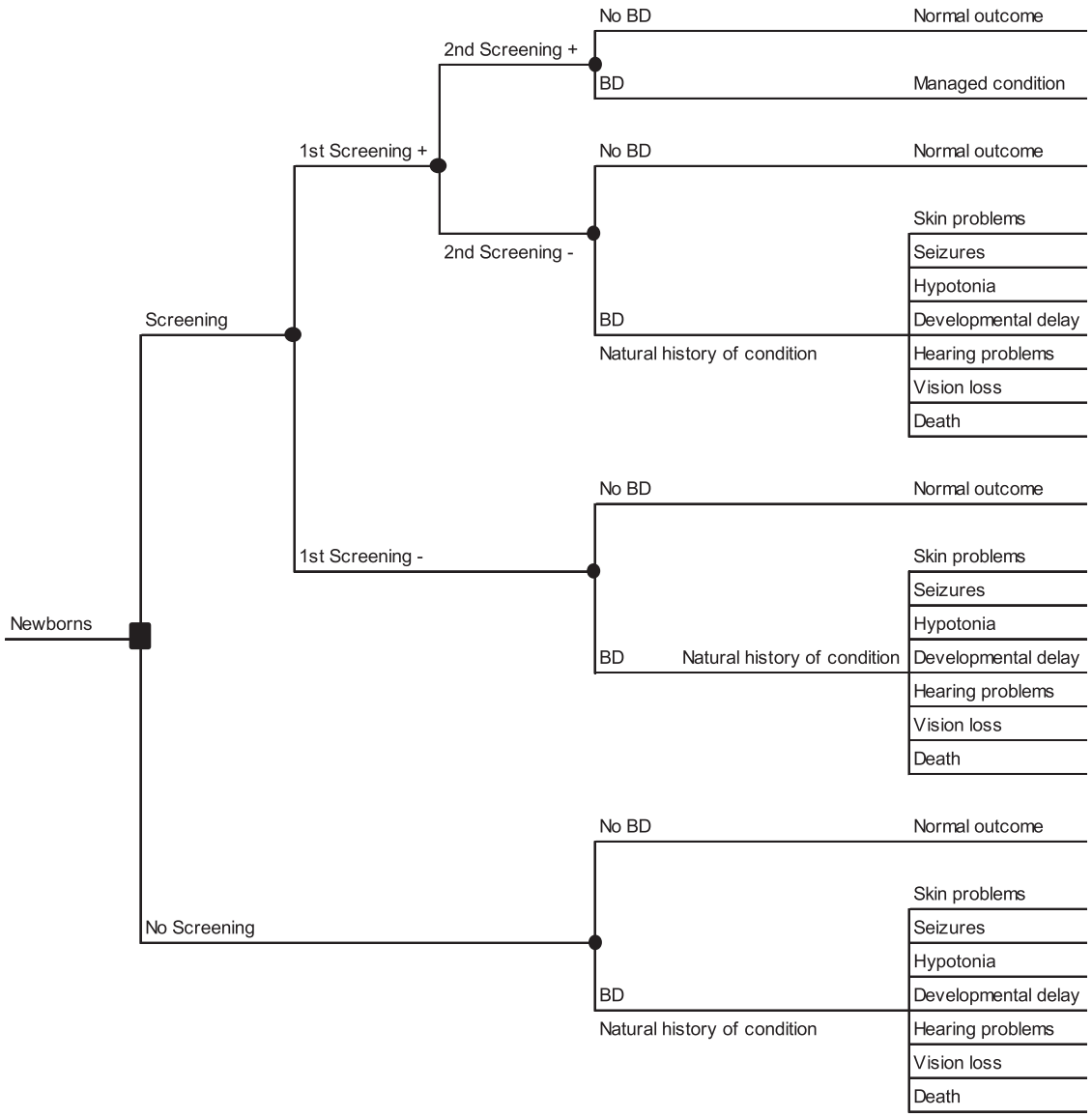

FIGURE 1
Simplified decision tree. Decision nodes represented by squares and chance node by circles.

individuals' life expectancy, and we applied a 3% discount rate to future costs and QALYs.[20]

Data

Probabilities

Data from the Galicia NBS program for BD were used to estimate some of the key parameters of the model (Table 1). From April 1987 to October 2013, 540 963 newborns were screened for BD, and 24 cases were detected: 16 cases with partial BD and 8 cases with profound BD. The recall rate observed was 0.44%. No false-negative cases were identified, but there were 35 false-positive cases in this period, yielding an estimated sensitivity and specificity of 100% and 99.99%, respectively. It is worth noting the possibility that the lack of false-negative cases might result from cases remaining undetected, and therefore the possibility of false-negative cases cannot be completely ruled out. However, these values are very similar to those reported in previous studies. Kwon and Farrell[21] estimated sensitivity and specificity rates in the United States between 1994 and 1995 of 100% and 99.98%, respectively.

A systematic review of international literature was undertaken to identify available evidence on the natural history of BD in the absence of a screening program and the effectiveness of NBS in terms of health outcomes among early detected patients (see Supplemental Information). We identified several case series that showed that patients with BD detected through NBS and under treatment remain asymptomatic.[7–10,13,22–24] Therefore, we assumed that BD cases detected

TABLE 1 Probabilities Related to BD Incidence, Screening Test, and Clinical Symptoms

	Value	SE	Source
Incidence of profound BD	1:67 620	0.00001	Galicia
Incidence of partial BD	1:33 810	0.00001	Galicia
Recall rate	0.00441	0.00011	Galicia
Sensitivity	1.00000	NA	Galicia
Specificity	0.99994	0.00001	Galicia
Negative predictive value	1.00000	NA	Galicia
Positive predictive value	0.40678	NA	Galicia
Clinical Outcomes Among Clinically Diagnosed Profound BD			
Seizures	0.564	0.046	22,25,27,29,30
Hypotonia	0.457	0.081	22,27,30
Skin problems	0.410	0.064	22,27,29,30
Hearing loss	0.515	0.044	6,8,22,27–30
Optic atrophy	0.175	0.034	8,26,27,29,30
Cognitive deficits	0.557	0.165	29,30
Death	0.064	0.026	25

Galicia data provided by the NBS program of the Galicia region. NA, not applicable.

through NBS and receiving treatment do not experience clinical symptoms. The probabilities of exhibiting symptoms in cases not detected by NBS are based on meta-analyzing the evidence from identified case series studies.[6,8,22,25–30] The probabilities of each outcome are presented in Table 1, including death, seizures, hypotonia, skin problems, cognitive deficits, optic atrophy, and hearing loss (see Supplemental Information for more details). The base case analysis assumes, conservatively, that only profound cases experience clinical complications, whereas in a separate analysis we allow for partial BD cases to also exhibit some of the features that have been documented in the literature among these patients (ie, seizures, skin problems, hearing loss, and cognitive deficits).

Our model allows any possible combination of symptoms, including no symptoms, and assumes that the probabilities of suffering each symptom are independent. Symptoms of untreated BD usually appear between 1 week and 10 years, with a mean age of 3.5 months.[3] We assume that acute episodes of seizures, skin problems, and hypotonia, when they occur, appear during the first year of life, whereas cognitive deficit, optic atrophy, and sensorineural hearing loss would become apparent in the second year of life, varying this last parameter between 2 and 15 years of age in the sensitivity analysis.

Resource Use and Unit Costs

BD screening requires measurement of biotinidase activity in blood-saturated filter paper samples on enzymatic assay or semiquantitative fluorometric determination. The cost of the screening test was estimated based on information provided by the NBS program in Galicia. We evaluate the cost-effectiveness of adding BD to a current NBS program, and therefore we considered only the extra resources needed specifically for BD testing. These resources include BD assays, equipment, and staff costs and yielded an estimated cost per test of $1.23 (Table 2).

The confirmatory tests consist of quantitative enzymatic determination of biotinidase activity in serum and plasma and the analysis of mutations of the biotinidase gene. Confirmed cases will then undergo testing of organic acids and determination of acylcarnitines in plasma. The unit costs of these tests are presented in Table 2.

Current recommendations for BD treatment involve a dose of oral biotin of 10 mg (ranging from 5 to 20 mg) per day for profound BD and a dose of 5 mg per week for partial BD. The following evaluations are generally recommended annually in profound cases and every 2 years in partial cases[1]: ophthalmologic, auditory, and medical geneticist or metabolic specialist evaluations and urinary organic acid and acylcarnitine analyses. Treatment and follow-up are assumed to be lifelong; unit costs are shown in Table 2. In our base case partial BD cases received treatment, because this is current practice in Galicia. Because there is controversy about whether partial BD cases ought to receive treatment, we also consider a scenario in which partial BD cases are not treated or followed up.

Existing but limited evidence on unscreened children detected after the onset of symptoms suggests that skin problems, seizures, and hypotonia rapidly resolve after biotin treatment, whereas some other features, such as developmental delay, optic atrophy, and hearing loss, are generally irreversible once they occur.[1,4] Therefore, we divided BD symptoms into acute and chronic symptoms, assuming that children affected by skin problems, seizures, and hypotonia would incur 1 hospitalization and standard BD diagnosis, treatment, and follow-up. Optic atrophy would require 1 additional visual testing for diagnosis, and once confirmed it would be addressed with extra annual ophthalmologic visits and evaluations. Children with hearing loss will undergo 1 additional auditory test, severe cases will need cochlear implants, and the rest would be treated with hearing aids, based on the proportions of profound and moderate hearing loss findings.[6] Hearing aids were assumed to be changed every 4 years up to 16 years of age and every 6 years thereafter. Additionally, patients with hearing loss would receive extra annual auditory evaluations with specialist and speech and language therapist visits. Cognitive deficits might involve a series of tests including MRI, electroencephalography, karyotype analysis, and array comparative

TABLE 2 Unit Costs and QALY Data

Unit Costs[a]	Value, $2013	Source
Screening		
Assay	$0.13	Galicia
Equipment[b]		
Chamber	$1633 ($0.01 per test)	Galicia
Dispensing pipetting system	$1225 ($0.01 per test)	Galicia
Spectrophotometer	$19 057 ($0.20 per test)	Galicia
Staff time[c]		
Laboratory technician	$0.79	Galicia
Senior laboratory manager	$0.07	Galicia
Total screening test cost	$1.23	Galicia
Diagnosis		
Extraction of blood sample	$5.39	HUC
Quantitative enzymatic determination	$136	CEDEM
Analysis of mutations gene *BTD*	$544	CEDEM
BD treatment and follow-up		
Biotin 5-mg 40 tablets	$4.95	33
Specialist visit	$145	31
Audiometry	$60	31
Visual acuity test	$21	31
Analysis of organic acids	$300	CEDEM
Analysis of acylcarnitines in plasma	$314	CEDEM
Treatment/diagnosis of BD symptoms		
Hospitalization International Classification of Diseases, Ninth Revision code: 266	$4990	32
PICU discharge status: Death	$26 063	32
Visually evoked potentials	$177	31
Brainstem evoked potentials	$439	31
Hearing aids	$1517	31
Cochlear implant	$53 709	50
MRI	$332	31
Electroencephalography	$113	31
Karyotype test	$231	31
Comparative genomic hybridization arrays	$836	51
Speech language therapist visit	$6.45	31
Dependency benefits (monthly)	$419	Royal Decree Act 20/2012

QALY Disutility	Median (SD)	Source
Mild seizure disorder	0.040 (0.009)	39
Mild hearing loss	0.010 (0.002)	39
Mild mental retardation	0.070 (0.018)	39

CEDEM, Centro de Diagnótico de Enfermedades Moleculares (Centre for the Diagnosis of Molecular Diseases); HUC, Hospital Universitario de Canarias (University Hospital of the Canary Islands). Galicia data provided by the NBS program of the Galicia region.

[a] Costs are expressed as the cost per service (eg, cost per test, cost per visit).

[b] Calculated based on the per annum number of tests run in Galicia in 2011 of 21 594. We applied discounting and annuitization assuming a 3% discount rate and a useful life of 5 y, using the methods reported by Drummond et al.[18]

[c] Calculated based on annual salaries provided by the NBS program for Madrid of $28 500 and $46 400 for laboratory technician and senior laboratory manager, respectively, and 185 min and 10 min per day for a laboratory technician and senior laboratory manager, respectively. We assumed 7.5 working hours per day and 250 working days per year to compute cost per minute.

genomic hybridization testing performed at time of diagnosis. If deficits were confirmed, these patients were assumed to visit the specialist annually. The cost of infant death was estimated based on the mean national cost of a PICU hospitalization with a discharge status of "death."

Whenever available, unit cost data were measured in terms of the mean of Spanish regional tariffs.[31] We also used national data published on the MSSSI Statistics Web site.[32] Unit costs of drugs were obtained from the database of the General Council of Spanish Pharmacists.[33]

In our base case we assume patients suffering chronic consequences of BD would not receive any disability benefits. However, permanent consequences of BD might mean patients are eligible to receive such benefits. Because eligibility is uncertain, we also evaluate the impact of assuming that 20% of the patients suffering chronic consequences of BD would receive disability benefits, and if they do, we conservatively assume that they would receive the lowest approved level of benefits (Table 2). Cost-effectiveness results including these costs are presented in a separate analysis.

Effectiveness Measure

QALY calculations are reported in detail in the Supplemental Information. In brief, we used QoL values related to BD complications taken from the literature and identified by a previous review.[34] Disutilities for BD complication based on the most conservative estimates are presented in Table 2; these were applied to the QoL population norm for Spain in our base case evaluation. We ran analyses with several different sets of utility weights.

Life expectancy of general Spanish population born in 2012[35] was applied to individuals who did not die of BD, with the exception of those with cognitive disorders, for whom we considered a lower life expectancy, based on data from Bittles et al,[36] applying the same approximation as used by Carroll and Downs.[37]

Sensitivity Analysis

We undertook a probabilistic sensitivity analysis by using 1000 simulations in a Monte Carlo analysis to compute cost-effectiveness acceptability curves (CEACs). CEACs indicate the probability that an intervention is cost-effective for different values of the willingness to pay for an extra unit of outcome.[38] We applied different probability distributions depending on the nature of the parameter.[38] Probabilities were characterized by a β distribution. Resource use data inputs were characterized with a γ distribution,

whereas uniform distributions were applied to unit cost parameters. In both cases, we used upper and lower limits of 20% around the mean values, with the exception of the cost of the test, which ranged from $0.7 (€0.5) to $3.4 (€2.5), and the age of the start of chronic features, which ranged from 2 to 15 years, with a uniform distribution. We used β distributions to characterize the uncertainty about the utility values.

RESULTS

The results of the analysis are presented in Table 3, showing the lifetime costs and QALYs for a Spanish birth cohort of 450 000 newborns with and without BD screening. Costs are shown separately for screening, diagnosis, BD treatment and follow-up, and costs of treating complications for the base case. Costs of disability benefits are also reported, although these costs are excluded from the base case, which also assumes that partial BD cases do not exhibit symptoms but are treated and followed up under the screening strategy and uses utility weights from Carroll and Downs.[39] The incremental total cost of BD screening compared with no screening in this case is estimated to be $557 044 (mean incremental cost per neonate of $1.24). The incremental QALY gain of BD screening is estimated to be 22.573 QALYs (mean QALY gain of 0.00005 per neonate), which leads to an ICER of $24 677 per QALY. When we consider less conservative scenarios, the cost per QALY is lower. This is especially the case when alternative sets of QALY weights are used, when disability benefits are included, and when the assumption that partial untreated cases do not exhibit any symptoms is relaxed. The latter scenario yielded estimated cost savings.

Figure 2 shows the CEACs computed based on the probabilistic analysis. At a threshold value of €30 000 per QALY (~$40 000), the probability that the screening strategy is the most cost-effective option reaches >70% in the base case.

DISCUSSION

Neonatal screening for BD has been instituted in several regions, including the following European countries: Austria, Belgium, Denmark, Germany, Hungary, Italy, the Netherlands, Sweden, and Switzerland.[40] BD screening is not currently done at the national population level in Spain. Our study made use of the ongoing experience of the NBS program in 1 Spanish region, which, alongside other sources, has allowed us to provide an estimate of the cost-effectiveness of adding BD to the national screening panel in Spain.

Previous evidence on the cost-effectiveness of BD screening is sparse. Carroll and Downs[37] undertook a cost-effectiveness analysis for NBS of a series of conditions in the United States, including BD. They found a program containing BD screening to be both more effective and less costly than a program not containing BD screening; however, they assumed the use of tandem mass spectrometry, which is not an appropriate technique for BD screening.[14] In Belgium, Schoos et al[41] also included BD among the diseases considered in their analysis, and they concluded that BD screening was cost-effective in the long term; however, health outcomes were not measured in this study.

Our study provides additional evidence of the cost-effectiveness of BD screening in the Spanish context, but our findings might be relevant in other settings. In the United Kingdom, where current policy is to not screen for BD, an external review conducted in 2012 emphasized the need of additional research on the prevalence of the condition and on the cost-effectiveness of newborn BD screening.[15] Although region-specific prevalence might only be estimated with pilot studies, this current evaluation might provide some broad indication of the likelihood of the cost-effectiveness of BD screening in similar settings.

TABLE 3 Base Case Estimates of Lifetime Costs and QALY Gains for BD Screening and No BD Screening for a Spanish Birth Cohort, Together With Incremental Analysis (Base Case and Cost per QALY of Additional Analyses)

	Screening	No Screening	Incremental (Screening Versus No Screening)
Screening costs	$559 740	—	$559 740
Diagnosis costs	$33 375	$4406	$28 969
Costs of BD treatment and follow-up	$367 417	$186 668	$180 748
Cost of treating complications	—	$212 413	−$212 413
Disability benefits	—	$532 440	−$532 440
Total cost (excluding disability benefits)	$798 795	$329 592	$469 203
Total cost (including disability benefits)	$798 795	$772 379	$26 417
QALY gain	22.573	—	22.573
Cost per QALY (Base case)			$24 677/QALY
Cost per QALY (Base case + Partial BD cases are not treated or followed up)			$16 507/QALY
Cost per QALY (Base case + Including disability benefits)			$14 510/QALY
Cost per QALY (Base case + Utility weights from Bennett et al[52])			$11 163/QALY
Cost per QALY (Base case + Utility weights from Petrou and Kupek[53])			$6367/QALY
Cost per QALY (Base case + Partial cases might exhibit symptoms)			Screening dominates[a]

[a] *Dominates* means that the strategy is less costly and more effective than the comparator.

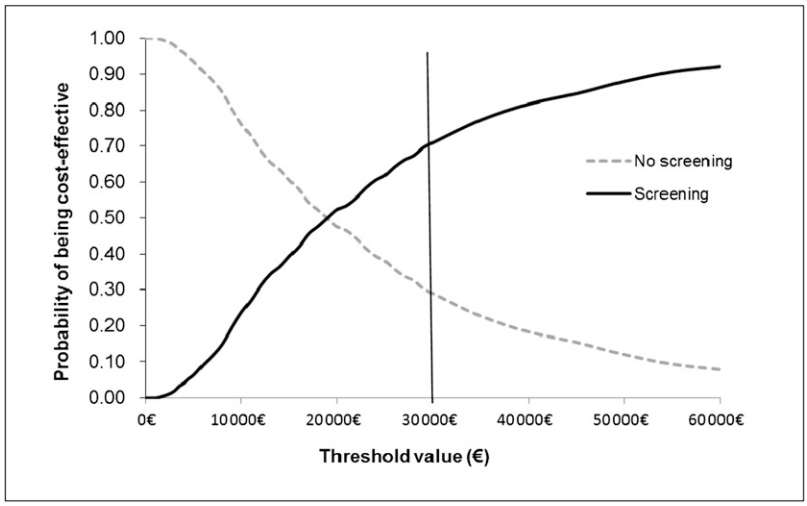

FIGURE 2
Cost-effectiveness acceptability curves. Note: Threshold value of €30 000 = US$40 000.

It is worth noting that data from the NBS program in the Galicia region shows higher BD prevalence than that reported in the worldwide study by Wolf.[5] However, other countries have shown similar, and sometimes higher, prevalence values, such as Canada,[42] Hungary,[24,43,44] Austria,[23,45] and Brazil.[9] We explored the implications of this issue by rerunning the analysis and assuming the same prevalence as that reported by Wolf. The conclusions remained the same: BD testing was found to be more cost-effective than clinical detection.

A critical issue around BD is the controversy as to whether identified partial cases ought to be treated with biotin supplementation. We found that identifying and treating both forms of BD is likely to be cost-effective, even if partial deficiency cases were assumed to not exhibit symptoms if untreated (which was our base case). The cost per QALY gained decreased only slightly when we assumed no treatment of partial BD cases. This finding, alongside the anecdotal evidence that some patients with partial BD do experience clinical symptoms if untreated,[22,30] and the lack of toxicity for biotin[1] build a stronger case for the treatment of detected partial BD.

This study has several limitations. BD is a rare disease, and therefore the information available on the natural history of the condition, the screening and treatment effects, and the health care resource implications is limited and of low quality. Information on long-term consequences of unscreened children is particularly sparse, although most evidence suggests that features related to cognitive, hearing, and vision problems are permanent. Few published cases have reported improvement to normal ranges,[46,47] which in some instances have been contradicted by long-term follow-up information.[48] Therefore, we could not estimate how often these complications are reversible, but we conducted an additional analysis imposing the strong assumption that these complications would last for a maximum of 5 years in every affected patient and then return to normal ranges. The ICER was affected by this assumption but was still under the reference cost-effectiveness threshold.

QALY measurement in newborn populations poses serious methodological challenges,[49] and so we also acknowledge the large degree of uncertainty with regard to these measures. Therefore, we used alternative sets of QALY weights, which were found to yield the same conclusions. Finally, the perspective of the analysis was that of the MSSSI; however, if a societal perspective were considered, wider costs related to BD should have been taken into account, such as patients' and carers' costs including parents taking days off work and productivity losses due to illness. Because BD screening would reduce clinical symptoms in identified newborns, accounting for these factors would probably increase savings related to the screening strategy, strengthening the conclusions of this article.

CONCLUSIONS

The inclusion of BD in the panel of conditions screened under the national NBS program in Spain is likely to be cost-effective compared with clinical detection. At standard threshold values, the probability that BD screening is cost-effective is >70%.

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ABBREVIATIONS

BD: biotinidase deficiency
CEAC: cost-effectiveness–acceptability curve
ICER: incremental cost-effectiveness ratio
MSSSI: Ministry of Health, Social Services and Equality
NBS: newborn screening
QALY: quality-adjusted life year
QoL: quality of life

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