METHODOLOGICAL CHALLENGES FOR THE ECONOMIC EVALUATION OF GENOMIC NEWBORN SCREENING: A SCOPING REVIEW

EE577

S. BAFFERT[1], J. COTTIN[1], T. ARCELIN[1], C. LEVEL[2], C. THAUVIN[2], L. FAIVRE[2], C. BINQUET[2], C. LEJEUNE[3,4]

1 – CEMKA, Bourg la Reine, France 2 – CHU de Dijon, Dijon, France 3 – Université Bourgogne Europe, Dijon, France 4 – CIC-EC Inserm 1432, CHU de Dijon, France

CONTEXT

- Rare diseases (RD) are frequently associated with long and complex diagnostic journeys, resulting in significant socioeconomic burdens for families as well as substantial direct costs for the healthcare system.
- Newborn screening (NBS), by enabling the early identification of RD and appropriate early management, has the potential to prevent long term complications related to delayed diagnosis and to reduce the costs associated with diagnostic wandering.
- At present, diseases are included in the NBS program one at a time, limiting the range of RD that can be addressed. Expanding NBS to include more genetic conditions has become a growing expectation. In contrast to targeted approaches, genome sequencing allows for the simultaneous analysis of thousands of genes responsible for a wide range of conditions.
- **Decision analysis and economic evaluations serve as a crucial decision-making aid for health policymakers by providing insights between the costs and benefits of expanding national NBS programs through genomic medicine (gNBS). However, conducting such analyses in the NBS context faces several methodological challenges.**

OBJECTIVES

We conducted a scoping review to explore the methodological approaches used in existing economic evaluations of NBS, aiming to provide an overview of current practices and highlight key methodological challenges.

METHODS

1 Definition of the research question and the objectives of the review

The literature review focused on two key dimensions:

Dimension 1	Dimension 2
Methodologies for assessing the **quality of life of infants and children** within the context of NBS	Methodologies and key structural choices of **studies and models conducted in NBS**

2 Conduct of the literature search

Initial search performed in **Medline via PubMed,** complemented by a review of general and specialized websites, including those of relevant international institutions (INAHTA, PEDE).

3 Screening and selection of identified studies

Inclusion criteria were predefined for each of the two dimensions of interest

Dimension 1	• Recommendations for measuring quality of life in infants. • Descriptions of specific quality of life measurement tools suitable for infants within a screening context.
Dimension 2	• Publications addressing methodological challenges related to NBS economic evaluation. • Recommendations for the robust conduct of economic evaluations of NBS. • Studies producing both a cost analysis and a health outcomes analysis in the context of NBS (French, European or American studies).

4 Extraction of relevant data

All collected documents were analyzed using a standardized grid, with a step by step approach to identify additional relevant sources within the selected articles.

5 Analysis, synthesis, and reporting of results

Synthesis established following the list of informational dimensions to be provided and mentioning the references of the sources used.

RESULTS

1 DIMENSION 1: Assessing the quality of life within a pediatric population

- Regarding health outcomes in economic evaluations, the most common summary measure is the **quality-adjusted life year (QALY)**, which is recommended by health authorities in cost-utility analyses wherever possible.
- **However, because HRQoL is difficult to assess in infants and young children and validated preference-based instruments adapted to these age groups are lacking, estimating health status utilities in these populations remains challenging[1].**
- Health status utilities for these populations are often **extrapolated from adult samples** or use adults as **proxy respondents** (parents, caregivers, etc.), each of which may introduce **bias or error**:
  → The validity of using structured questionnaires base on adult-derived utility weights for children's health states is questionable.
  → Parents/caregivers can be reliable reporters for physical activity limitations and externally manifest symptoms of illness but are less reliable for subjective QoL aspects such as mood and emotion.
- As an alternative to these challenges, **published pediatric utility weight catalogues** can be consulted, but discrepancies among them raise concerns and highlight the importance of conducting sensitivity analyses.

It should be noted that new preference-based HRQoL instruments for young children are emerging and may address many of the limitations of existing tools:

- ❑ **Infant Quality of Life Instrument (IQI)** for infants aged 0 to 1 year (has been used notably in several studies involving NICU infants)[2,3,4].
- ❑ **EuroQol Toddler and Infant Populations (EQ-TIPS)** for the 0-3 years subgroup (still under development)[5].

2 Methodologies and key structural choices of models conducted in NBS

- Economic evaluations of NBS encounter multiple methodological challenges, as identified in several literature reviews[6,7,8,9].
- Notably, in economic evaluations of NBS, there is critical need to define a **comprehensive scope of costs** that encompasses the **societal benefits of screening** and the **externality effects** associated with it. Patient-related costs should include[10]:

Direct medical costs	Direct non-medical costs	Indirect costs
Screening costs, treatment costs, downstream health costs (monitoring and management of detected cases)	Travel expenses, parental time costs, costs associated with institutional care and special education…	Costs due to **lost productivity** These costs should encompass both lost **parental** wages and potential losses incurred by **patients** upon reaching adulthood

- Adopting a **societal perspective** typically implies the adoption of a **lifetime time horizon**, as insufficient early care for rare disease–affected newborns can lead to lifelong consequences, including income losses resulting from severe deficiencies that limit their future opportunities and employability. However, assessing such long-term outcomes related to conditions screened in newborns represents another significant challenge due to the scarcity of data on long-term outcomes[2].
- A scoping review of economic evaluations of NBS (35 studies included) highlights the challenges of fulfilling these criteria[11]:
  → **Perspective**: societal perspective in only 8 studies (23%).
  → **Time horizon**: lifetime horizon in only 10 studies (29%). The prevalence of relatively short time horizons in most studies may be attributed to the difficulties in collecting long-term evidence to populate the models.
  → **Costs**: none of the studies considered all the relevant categories of costs recommended, indicating that comprehensive cost accounting is a problematic aspect of economic evaluations in the NBS field. Many studies adopting a societal perspective also failed to include productivity losses.

Point for reflection

In light of all these different methodological challenges, several authors have established a framework for evaluating the efficiency of NBS and have proposed several key considerations for conducting such studies[8,10,12].

- ❑ Given the many limitations of various approaches to individual valuation of a child's health and the importance to capture broader costs, adopting a '**family perspective**' may be a viable option, as it more accurately reflects how children's health states are experienced within the family unit and allows for capturing the costs linked to parental/patient productivity loss.
- ❑ However, this approach remains little explored and is not generally accepted by the French National Authority for Health (HAS), with the collective perspective (requires the use of production costs) being the reference for economic evaluations in France.

CONCLUSION

Economic evaluations are valuable tools for informing decision makers about the balance between costs and benefits of expanding gNBS of rare diseases. However, multiple methodological challenges specific to the economic evaluation of NBS have been identified in several literature reviews. Overcoming these challenges is crucial for producing relevant assessments of the long-term health outcomes, costs, and quality of life associated with gNBS.

COI :
- *The study was sponsored by CHU Dijon.*
- *BAFFERT S., COTTIN J. and ARCELIN T. are employees at CEMKA, a French consulting firms in the field of evaluation of products, programs and organizations in Health.*
- *LEVEL C., THAUVIN C., FAIVRE L., BINQUET C. are employees at CHU Dijon.*
- *LEJEUNE C. is an employee at Université Bourgogne Europe and at CHU Dijon.*

REFERENCES
[1] Ungar WJ. Challenges in health state valuation in paediatric economic evaluation: are QALYs contraindicated? Pharmacoeconomics. 2011 Aug;29(8):641-52. doi: 10.2165/11591570-000000000-00000. PMID: 21604821.
[2] Jabrayilov R, et al. A descriptive system for the Infant health-related Quality of life Instrument (IQI): Measuring health with a mobile app. PLoS One. 2018 Aug 31;13(8):e0203276.
[3] van Dokkum Nh et al. Early stress during NICU stay and parent-reported health-related quality of life after extremely preterm birth: an exploratory study with possible targets for early intervention. Front Pediatr. 2024 Apr 8;12:1381008. doi: 10.3389/fped.2024.1381008. [4] Heuvink P, et al. Parent-Reported Health-Related Quality of Life (HRQoL) of NICU Graduates in Their First Year: A Prospective Cohort Study. Int J Environ Res Public Health. 2025 Mar 17;22(3):447. doi: 10.3390/ijerph22030447.
[5] https://euroqol.org/research-at-euroqol/eq-tips/
[6] Baple, E. et al. Exploring the benefits, harms and costs of genomic newborn screening for rare diseases. Nat Med 30, 1823–1825 (2024).
[7] Prosser LA et al. Decision analysis, economic evaluation, and newborn screening: challenges and opportunities. Genet Med. 2013;14(8):703-712.
[8] Sparks TN, Caughey AB. How should costs and cost-effectiveness be considered in prenatal genetic testing? Semin Perinatol. 2018 Aug;42(5):275-282. doi: 10.1053/j.semperi.2018.07.003. Epub 2018 Jul 26.
[9] Grosse, S. D. et al. (2021). Newborn screening for congenital hypothyroidism and congenital adrenal hyperplasia: the balance of benefits and costs of a public health success. International Journal of Neonatal Screening, 7(3), 37. https://doi.org/10.3390/ijns7030037
[10] Langer, A et al. (2012). Specific guidelines for assessing and improving the methodological quality of economic evaluations of newborn screening. BMC Health Services Research, 12(1), 338. https://doi.org/10.1186/1472-6963-12-338
[11] Cacciatore, P., et al. (2020). The Methodological Quality and Challenges in Conducting Economic Evaluations of Newborn Screening: A Scoping Review. International Journal of Neonatal Screening, 6(4), 94. https://doi.org/10.3390/ijns6040094
[12] Ferket BS, et al. Cost-effectiveness frameworks for comparing genome and exome sequencing versus conventional diagnostic pathways: A scoping review and recommended methods. Genet Med. 2022 Oct;24(10):2014-2027.