BIOCHEMICAL OR GENETIC SCREENING FOR MSUD? A REAL-WORLD EXPERIENCE AND SCOPING REVIEW

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INTRODUCTION

Newborn screening (NBS) enables the early diagnosis of metabolic diseases, but MS/MS has limitations in sensitivity and specificity. The use of exome/genome sequencing broadens the diagnostic potential of NBS, but has challenges such as variants of uncertain significance and the risk of false negatives.

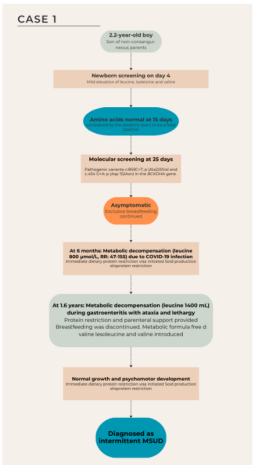
OBJECTIVE

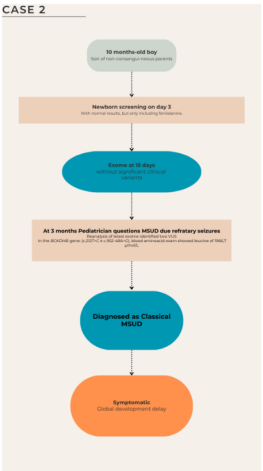
To highlight decision points between biochemical and genetic screening in Maple Syrup Urine Disease (MSUD) through two case reports of MSUD.

We also present a scoping review on the challenges of genetic and molecular newborn screening in non-classical MSUD, conducted in accordance with the PRISMA-ScR and Joanna Briggs Institute guidelines. The search strategy is available through the QR code:

RESULTS

1. **Case reports**





2. **Scoping review**

A total of 101 articles were initially identified. After applying the eligibility criteria, 11 studies were retained for analysis. The PRISMA flow diagram is available in figure 1.
Table 1 summarizes the selected studies.

Figure 1. PRISMA flow diagram

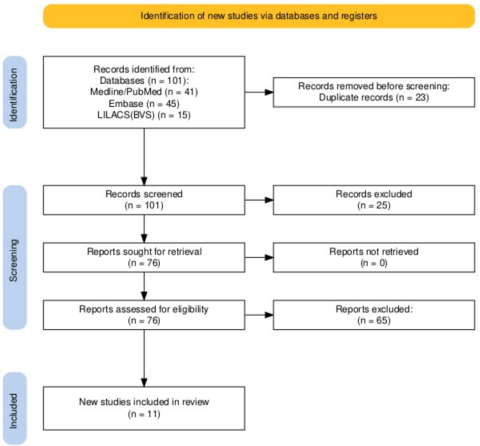


Table 1. Summary of studies

Study	Year	Country	Tipo de estudo	Principais achados
Upadia, et al	2025	USA	Case report (one case)	Tiamine-responsive MSUD not detected by NBS; pathogenic DBT variants.
Singh, et al	2024	USA	Case report (Two Cases)	*BCKDK,* p.Thr372Arg with biochemical MSUD phenotype but asymptomatic; dominant inheritance.
Chen, et al	2023	China	Population-based NBS	NBS of 1.3M newborns em Xangai, China: 6 MSUD confirmed; high false-positive rate; best markers Xle, Xle/Phe, Xle/Ala.
Lin, et al	2023	China	Case report (one case)	Intermediate MSUD; NBS inconclusive, diagnosis by *BCKDHB* genetic testing.
Magnolo, et al	2022	Italy	Case report (one case)	GOF mutation in *BCKDK* (p.His162Gln) → persistent BCAA elevation, no clinical symptoms.
Chin, et al	2022	Australia	Case report (one case)	Intermediate MSUD missed by NBS; DBT variants (VUS + likely pathogenic); confirmed by functional testing.
Pode-Shakked,et al	2020	Multiple	Case series (8 patients)	8 patients, 4 families with intermittent MSUD; variable clinical presentation; new variants in *DBT/BCKDHB* genes.
Stroek, et al	2020	Netherlands	Population-based NBS	11y Dutch NBS: ~2M newborns, 4 MSUD confirmed; high false-positive rate; ratios improved PPV.
Puckett, et al	2010	USA	Population-based NBS	California NBS failed to detect variants; alo-isoleucine testing could improve sensitivity.
Bhattacharya, et al	2024	USA	Population-based NBS	Texas NBS: 2nd screen identified cases missed by 1st; case with *BCKDHA* variant initially VUS.
Margutti , et al	2020	Brazil	Case series (21 patients)	21 Brazilian patients; genetic heterogeneity; frequent delayed diagnosis; majority with one pathogenic variant.

MSUD: Maple Syrup Urine Disease. GOF: Gain of Function. VUS: Variant of Uncertain Significance. PPV: Positive Predictive Value.Xle: combined leucine/isoleucine measurement.. Xle/Phe: ratio of leucine/isoleucine to phenylalanine..Xle/Ala: ratio of leucine/isoleucine to alanine.

DISCUSSION

Our cases, together with data from the literature, highlight the heterogeneity of MSUD and the limitations of biochemical NBS, which may yield false positives or negatives. An integrated approach with biochemical markers, second-tier tests, and genetics is essential for timely and accurate diagnosis.

REFERENCE