

Newborn screening for urea cycle disorders

An evidence map to outline the volume and type of evidence related to newborn screening for urea cycle disorders for the UK National Screening Committee

Version: 4.0

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Date: June 2025

The UK National Screening Committee secretariat is hosted by the Department of Health and Social Care

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About the UK National Screening Committee (UK NSC)

The UK National Screening Committee (UK NSC) advises ministers and the N H S in the 4 UK countries about all aspects of [population](#) and targeted screening and supports implementation of screening programmes.

Conditions are reviewed against [evidence review criteria](#) according to the UK NSC's [evidence review process](#).

Read a [complete list of UK NSC recommendations](#).

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www.gov.uk/uknsc

Blog: <https://nationalscreening.blog.gov.uk/>

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Summary

This document discusses the findings of an evidence map completed by the University of Bristol Evidence Synthesis for Screening (BESS) Group on newborn screening for urea cycle disorders (UCDs).

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. They inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration.

Based on the findings of this evidence map, the authors' recommendation is that current evidence does not support the commissioning of further synthesis work on newborn screening for UCDs at the present time, as it is unlikely that the findings would be significantly different to this evidence map.

Introduction and approach

Importance of evaluating potential screening programmes

*“All screening programmes do harm. Some do good as well and, of these, some do more good than harm at reasonable cost.”*¹ Screening programmes aim to identify people at risk at a stage that optimises the chances of effective treatment and improved patient outcomes. The UK National Screening Committee (UK NSC), a committee of independent experts, plays a critical role in determining whether the benefits of a potential screening programme outweigh the harms and justify the associated costs. UK NSC recommendations are based on careful review of evidence against specific [criteria](#).

Several factors affect whether a screening programme is clinically and/or cost effective. These include people’s access to and uptake of screening, test accuracy, ease of use, cost and administration, whether the intervention leads to better outcomes compared with treating once symptoms develop, and any other unintended consequences.¹ It is essential to consider the harms that may result from false positives, false reassurance, overtreatment, and complications from tests or treatments. Critically, it cannot be assumed that screen-detection always leads to improved patient outcomes.¹ Overdiagnosis, where screening detects an abnormality that would not have caused symptoms or harm, is an important risk. Comprehensive evaluation of screening programmes acknowledges key biases that include healthy screenee bias, lead or length time biases, and overdiagnosis bias.¹ Ethical concerns include the need for informed consent, as well as impact on health inequalities, if some groups are less able to access screening,² and the potential strain on NHS services if the workload of screening worsens access to care for symptomatic patients.

Background and objectives

The UK NSC external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed [online](#).

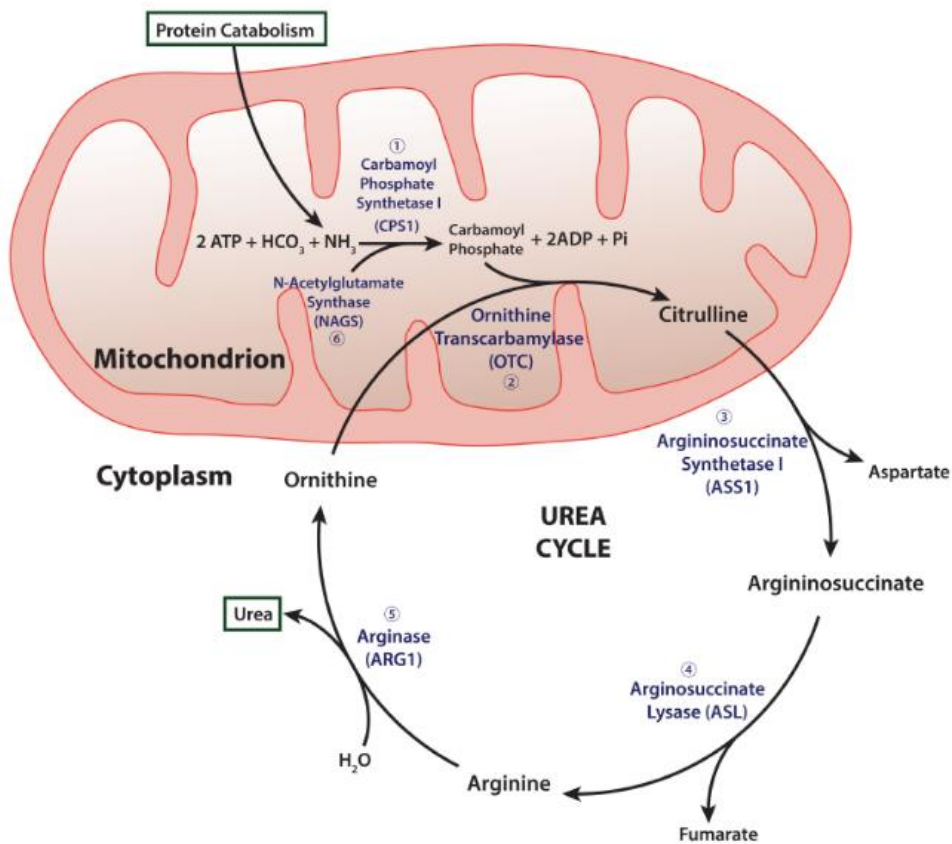
This is the first time that screening for all Urea Cycle Disorders (UCDs) has been considered by the UK NSC. In 2015, the UK NSC commissioned a review which focused exclusively on screening for citrullinaemia (ASS1 deficiency) and argininosuccinic acid lyase (ASL) deficiency. It found that there were concerns over the reliability and the timing of the test, particularly in relation to the presentation of the acute forms of the conditions. For ASL deficiency, in particular, the review noted that it was unclear whether the treatment is successful in preventing the development of neurocognitive deficiencies and liver disease, even if metabolic decompensations are avoided.³

A proposal for newborn screening for UCDs, specifically for ornithine transcarbamylase (OTC) deficiency, was submitted to the UK NSC during the 2022 annual call for topics. The proposal was considered by an evaluation group which included the UK NSC chair, the chairs of the UKNSC’s Fetal, Maternal and Child Health group and Adult Reference Group, patient and public voice members and the UK NSC evidence team. After consideration, it was agreed that work should be undertaken to assess the topic of newborn screening for urea cycle disorders in the form of an evidence map.

Description of UCDs

Urea Cycle Disorders (UCD) are a group of inherited metabolic conditions caused by a deficiency of 1 of the main 6 enzymes in the urea cycle. The urea cycle biochemical pathway occurs primarily in the liver and is responsible for the removal of nitrogen waste from the breakdown of proteins, ultimately producing urea from ammonia,^{4, 5} (see Figure 1). The urea cycle is also the sole source of endogenous production of the amino acids arginine, ornithine and citrulline.⁴ The cumulative incidence of all urea cycle disorders has been estimated as 1 in 35,000 live births,⁶ although more recent studies have estimated a lower cumulative incidence of around 1 in 51,946 live births.⁷

Figure 1: Outline of the urea cycle



The main 6 enzymes involved in the pathway are numbered 1 to 6, with their associated gene in brackets. Source: Blair et al. 2015⁵

The main 6 enzymes that are deficient in UCDs are:

- Carbamoylphosphate synthetase I (CPS1)
- Ornithine transcarbamylase (OTC)
- N-acetyl glutamate synthetase (NAGS, cofactor-producing enzyme)
- Argininosuccinic acid synthetase (ASS1, also known as citrullinemia type 1, or CIT)
- Argininosuccinic acid lyase (ASL, also known as argininosuccinic aciduria, or ASA)
- Arginase (ARG1, also known as argininemia)

2 additional secondary urea cycle disorders are also recognised in the literature, these are due to inherited deficiencies of 2 amino acid transporters also involved in the urea cycle: ornithine translocase (ORNT1: ornithine/citrulline carrier) and citrin (aspartate/glutamate carrier, also known as citrullinemia type II or CIT2).⁴

Presentation of UCDs

OTC, CPS1 and NAGS deficiencies are known as 'mitochondrial UCDs' (sometimes also referred to as "proximal" UCDs) because of their position in the urea cycle, whereas ASS1, ASL and ARG1 deficiencies are recognised as 'cytosolic UCDs' (sometimes also referred to as "distal" UCDs). OTC deficiency is the most common form of urea cycle disorder.^{8, 9} Unlike the other UCDs, which are recessive, OTC deficiency's inheritance is X-linked which means that it manifests mostly in males. Female heterozygotes can be symptomless though they can show considerable variation in clinical symptoms, including debilitating and life-threatening hyperammonaemia.^{5, 8}

Severe deficiency or total absence of any of the first 4 enzymes in the urea cycle (CPS1, OTC, ASS1, ASL) or the cofactor NAGS, results in the rapid accumulation of ammonia during the first few days of life and the development of related symptoms such as vomiting, anorexia and lethargy which rapidly progresses to encephalopathy, coma and death if untreated.⁴ In cases where there is only a partial deficiency of these enzymes, or in arginase deficiency (the final enzyme in the pathway), symptoms tend to be milder and manifest after the newborn period, sometimes only in adulthood. In these instances, ammonia accumulation may be triggered at almost any time by illness or stress (e.g. surgery, prolonged fasting, excessive protein intake, peripartum period).⁴

Manifestations at any age can lead to brain injury or death from hyperammonaemia. It is recognised that the age and severity of presentation depends on multiple factors such as the causative mutation, the residual enzyme activity as well as physiological and environmental influences and that differences in the severity of presentation may also occur in affected families.⁸

Screening and diagnosis of UCDs

Newborn screening requires the presence of a suitable marker to indicate the likely presence of the condition. Hyperammonaemia is the hallmark of UCDs, but high ammonia concentrations are not specific enough to lead to a diagnosis of UCD and each UCD has its own biochemical profile. Glutamine is another metabolite that is generally elevated in UCDs but is highly unstable, making it unsuitable as a screening marker. Similarly, orotic acid, though often elevated in the urine of patients with OTC deficiency, cannot be used as a marker in blood.¹⁰ Therefore, testing for UCDs usually involves a combination of biochemical analyses: quantitative plasma amino acids analysis, urine organic acid and orotic acid analysis, and urine amino acid analysis can be used to arrive at a tentative diagnosis and can help to distinguish between the different types of UCD.^{4, 8} In recent years, the use of postanalytical interpretive tools such as ratios of metabolites has been suggested as a way to improve the sensitivity and specificity of newborn screening strategies for several UCDs, though this is under investigation.¹⁰ Molecular genetic testing is the primary method of diagnostic confirmation for all UCDs.^{4, 8}

Treatment of UCDs

In the acute phase, the treatment of individuals with UCDs requires reducing the plasma ammonia concentration quickly, for example by haemofiltration, nitrogen scavenger therapy (sodium phenylacetate and sodium benzoate) for bypassing the urea cycle, stopping protein intake, improving the catabolic state through caloric supplementation of glucose, citrulline and arginine amino acid and liver transplantation.^{4, 8, 11} Liver transplantation does not reverse neurologic compromise, but it can help to normalise ammonia levels and to eliminate the need for dietary restrictions or nitrogen-scavenging medications.¹¹ The long-term management of individuals tends to be tailored according to the severity of the condition, previous decompensation, and protein tolerance. Some adults with mild UCDs may only require preventive measures during acute illness or surgery, while others might instead require a lifelong protein-restricted diet and ammonia scavenging agents.⁸

Increasingly, there have been efforts to explore the potential of RNA-based medicines for UCDs and the development of gene editing applications targeting specific gene defects and enzymes in the urea cycle.¹² In the case of OTC deficiency for example, some of these new therapeutic approaches have shown proof of concept and are currently being tested in clinical trials.¹³

Current guidance on screening for UCDs

Currently, no country implements universal newborn screening for all UCDs and the UK does not include any UCDs in its newborn screening programme.¹⁴ When screening is conducted, it typically targets only the cytosolic UCDs. Examples of countries which have implemented newborn screening for specific UCDs are provided in Table 1. This does not necessarily mean that an end-to-end quality assured screening programme is in place in these locations.

The limited adoption of newborn screening for UCDs is partly due to concerns about its effectiveness in detecting severe mitochondrial forms of the disorder. In such cases, dangerously high levels of ammonia (hyperammonaemia) and serious symptoms can develop within days after birth.¹⁰ It is consequently acknowledged that patients with severe or total enzyme deficiency will most likely have significant hyperammonaemia by the time the screening results are available, unless already diagnosed and treated on the basis of their clinical presentation and/or family history. In other words, these patients may not stand to benefit from newborn screening.¹⁰

In 2015, the Royal College of Paediatric and Child Health (RCPCH) in the UK published a clinical guideline for the management of children and young people with an acute decrease in conscious level.¹⁵ This guideline had input from specialists in inherited metabolic disorders and recommends that ammonia testing is carried out in all children and young people with a decrease in conscious level. However, measures to improve diagnosis are a separate intervention to the delivery of a screening programme. Screening is not an effective way of promoting diagnostic vigilance and may have the opposite effect.¹

Metabolic Support UK have compiled a series of UK-specific resources to raise awareness with healthcare professionals to help them in the diagnosis, testing and treatment of hyperammonaemia to improve outcomes.¹⁶

Table 1: UCD specific newborn screening by country

The source of information relating to screening is provided as references per country. This table is not intended to be an exhaustive list, but rather examples of countries performing UCD screening.

	CPS1	OTC	ASS1	ASL	ARG1	NAGS	ORNT1	CIT2
European Economic Area (EEA)								
Austria ¹⁴								
Czech Republic ¹⁷								
Denmark ¹⁴								
Estonia ¹⁴								
Finland ¹⁴								
Hungary ¹⁴								
Iceland ¹⁸								
Italy ¹⁴								
North Macedonia ¹⁸								
Portugal ¹⁴								
Poland ¹⁴								
Slovakia ¹⁴								
Slovenia ¹⁴								
Spain ¹⁴								
Sweden ¹⁴								
International / non-EEA countries								
Australia and New Zealand ¹⁹								
Canada ²⁰								
China ²¹								
Iran ²²								
Israel ¹⁸								
Philippines ²³								
Quatar ²⁴								
Russia ¹⁴								
Saudi Arabia ²⁵								
Taiwan ²⁶								
Ukraine ¹⁸								
US ²⁷								
Uzbekistan ¹⁸								

Green boxes indicate nationally implemented newborn screening.

Yellow boxes indicate countries in which newborn screening for UCDs differs regionally.

Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic.

This evidence map has been developed to assess whether a more sustained review on newborn screening for UCDs should be commissioned in 2025 and to evaluate the volume and type of evidence on key issues related to newborn screening for UCDs.

The aim was to address the following questions:

1. Are there any national or international guidelines or recommendations on newborn screening for UCDs?
2. What is the volume and type of evidence on the accuracy of newborn screening strategies for UCDs using dried blood spots?
3. What is the volume and type of evidence available on the benefits and/or harms of interventions in asymptomatic and/or presymptomatic children with UCDs identified through screening? i.e. does early initiation of treatment following screen detection provide better outcomes for UCDs compared with initiation of treatment following clinical detection?

The findings of this evidence map will provide the basis for discussion to support decision-making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on newborn screening for UCDs in 2025.

The aim of this document is to present the information necessary to inform UK NSC decision-making processes.

Search methods and results

Detailed methods, including eligibility criteria and search strategies, are available in Appendix 1.

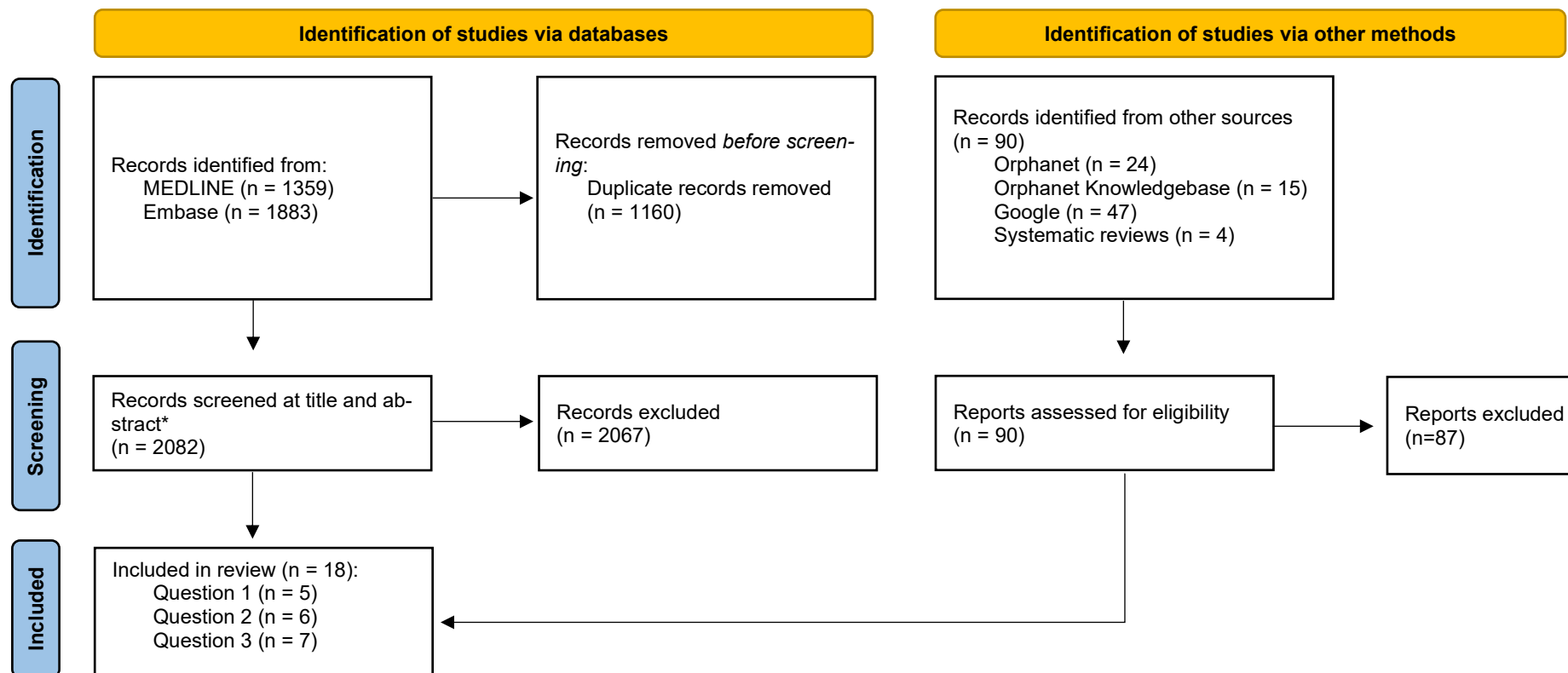
The searches were conducted on 23 April 2025 in 2 databases: MEDLINE and Embase. For question 1, the following were also searched: Orphanet on 30 April 2025 (www.orpha.net), Orphanet Newborn Screening Bibliographical Knowledge base on 6 May 2025 (nbs.orphanet.app) and Google on 8 May 2025. The reference lists of relevant systematic reviews identified by the searches were screened for any additional relevant studies. Deduplication was conducted manually and automatically using EndNote and Nested Knowledge® (nested-knowledge.org). The search period was restricted to January 2015 to May 2025.

Titles and abstracts were screened by 1 reviewer. A random sample of 20% of records were independently screened by a second reviewer. The remaining 80% were screened using the AI screening model (Robot Reviewer) integrated in Nested Knowledge®. All references were reviewed at abstract level. As this was an evidence map, only 'top level' study information was extracted. Full texts were often reviewed to clarify uncertain pieces of information, both to assess eligibility and extract relevant data. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

Abstract reporting tables are available in Appendix 2. The database searches returned 3,242 results, the additional searches in Orphanet and Google retrieved 86 results. 4 relevant systematic reviews identified through the searches were also screened for additional studies. After automatic and manual de-duplication, 2,172 unique references were reviewed for relevance to the review questions. Eighteen reports were included. A flow diagram summarising the flow of studies through the evidence map is presented in Figure 2.

Figure 2: PRISMA flow diagram²⁸

*Studies were assessed for eligibility by screening title and abstracts as this was an evidence map. However, full texts were consulted where eligibility could not be clearly ascertained from the study title or abstract.



Summary of findings

Question 1: Are there any national or international guidelines or recommendations on newborn screening for UCDs?

Five documents were included for this question (Table 2 and Appendix 2).²⁹⁻³³ No evidence was identified relating to a UK setting.

Two documents provided expert panel consensus recommendations on newborn screening for UCDs, developed by metabolic specialists, biochemists, and other clinicians.^{29, 30} One was an international guideline covering Israel and 8 countries in Europe; the other focused specifically on Italy. The international guideline recommended newborn screening for ASL and ASS1 only, citing insufficient published evidence for screening other UCDs such as NAGS, CPS1D, OTC, and ARG1.²⁹ In contrast, the Italian recommendations supported newborn screening for all UCDs.³⁰ However, given its Italian healthcare context, applicability to the UK setting may be limited. These recommendations are based on expert opinion and have not necessarily followed a robust process of assessing evidence against explicit criteria. Also, they are concerned with an offer of testing, rather than on defining, delivering and monitoring an end-to-end quality assured screening programme. Both documents also included guidance on the diagnosis and management of UCDs.

The remaining 3 documents were UCD-specific “action reports” published by the American College of Medical Genetics and Genomics. These reports were less relevant to this evidence map, as they outlined steps to take after a positive screening result but did not include recommendations about implementing UCD newborn screening.³¹⁻³³

Table 2: Overview of the 5 included for question 1

Study	Country	Guidance type	UCD	Purpose
Haberle et al., 2019 ²⁹	Israel and 8 countries in Europe (unspecified)	International guidelines from expert clinical panel consensus	Any	Screening, diagnosis, and management of UCDs
Burlina et al., 2023 ³⁰	Italy	National recommendations from expert clinical panel consensus	Any	Screening, diagnosis, and management of UCDs
ACMG, 2022 ³¹	US	National “action reports” from the ACMG	ARG1	Management of UCD following a positive newborn screening result.
ACMG, 2022 ³²			CIT2, ASL, ASS1	
ACMG, 2021 ³³			NAGS, OTC, CPS1	

Abbreviations: ACMG = American College of Medical Genetics and Genomics

In summary, only 2 documents were identified which made recommendations on newborn screening for the detection of UCDs. These were expert panel recommendations that were concerned with an offer of testing for some UCDs, rather than on defining, delivering and monitoring an end-to-end quality assured screening programme. There is currently insufficient relevant guidance on screening to justify commissioning an evidence summary on this question.

Question 2: What is the volume and type of evidence on the accuracy of newborn screening strategies for UCDs using dried blood spots?

Six studies were included for this question (Table 3 and Appendix 2).³⁴⁻³⁹ The objective of all studies was to evaluate pilot or established screening programmes, but studies also provided data that allowed the calculation of some measure of the accuracy of tests for UCDs. All studies used a single-gate design and were conducted in newborns who were enrolled in screening programmes. No studies were conducted in the UK.

One study was conducted within the context of a pilot newborn screening programme later implemented in Hong Kong,³⁶ 3 were conducted in established programmes in Hong Kong, Taiwan and Denmark,^{34, 35, 37} and 2 were conducted in established screening programmes which were considering adding specific UCDs to existing screening programmes in Germany and Israel.^{38, 39} Four of the studies were overall evaluations of expansion of NBS to include multiple new target conditions (IEMs), not specifically UCD screening.

Three studies reported on the accuracy of tests for the single secondary UCD, CIT2.³⁴⁻³⁶ The other 3 studies reported accuracy measures for newborn screening strategies targeting combinations of 2 or 3 different UCDs (CIT2, ARG1, ASS1, ASL, OTC, and CPS1).³⁷⁻³⁹ No studies were identified that evaluated the accuracy of screening strategies for the detection of NAGS or ORNT1-type UCDs. Although total sample sizes were large (range 15,138 to 1.77 million) the number of cases of UCDs was very low (<20 cases per study), reflecting the rarity of these conditions.

All 6 studies reported numbers of people testing positive for UCDs, stratified by whether they were also positive on the reference standard or not (i.e. true positives and false positives). Three studies reported positive predictive values (PPVs) for specific UCDs: ASS1 (43%),³⁸ CIT2 (14.3%),³⁴ and OTC (12.72%).³⁹ Three studies, reported data from which PPVs could be calculated for specific UCDs (ASS1, ASL, ARG1, CPS1, and CIT2), but did not actually report PPVs.^{36, 37, 39} One study did not report PPV, but did report improved PPV for CIT2 after the addition of second tier testing.³⁵ Asymptomatic and/or presymptomatic newborns with normal screening results did not undergo confirmatory testing in any of the studies. Three studies indicated that the detection of false negatives depended on voluntary reporting to the screening programmes,³⁴⁻³⁶ while the follow-up methods for negative cases in the remaining 3 studies were not clearly described. Those who tested negative on screening and were then subsequently diagnosed as having a UCD following clinical presentation were identified as false negatives. It is likely that not all false negative cases would be identified during the follow-up periods, which ranged from 1 to 7 years, as some cases of UCD do not present clinically until adulthood. Additionally, some clinically diagnosed cases may not have been reported back to the newborn screening programmes and so may not have been identified as false negatives. This partial verification is likely to have resulted in underestimation of false negatives and overestimation of true negatives, meaning sensitivity and specificity could not be reliably assessed.

Table 3: Overview of 6 studies included for question 2

Study	Country	Follow-up	Size	UCD	Number with UCD	Index test	Reference standard
Belaramani et al., 2024 ³⁴	Hong Kong	7 years	125,688	CIT2	8	Tandem-MS	Genetic*
Chen et al., 2022 ³⁵	Taiwan	7 years	753,520	CIT2	16	Tandem-MS / genetic	Unclear
Lam et al., 2020 ³⁶	Hong Kong	1 year	15,138	CIT2	2	Tandem-MS	Genetic*
Lund et al., 2020 ³⁷	Denmark	7 years	967,780	ARG1	0	Tandem-MS	Biochemical and genetic*
				ASL	4		
				ASS1	2		
Maier et al., 2023 ³⁸	Germany	Unclear	1.77 million	ASS1	9	Tandem-MS	Biochemical and genetic*
				CIT2	0		
Staretz-Chacham et al., 2021 ³⁹	Israel	6 years	1.15 million	ASL	2	Biochemical	Genetic*
				ASS1	6		
				CIT2	1		
				CPS1	3		
				OTC	6		

Abbreviations: Tandem-MS = tandem mass-spectrometry; * The reference standard was only performed when the screening results were positive.

In summary, the volume of evidence on the accuracy of newborn screening for UCDs is limited. We identified 6 single-gate studies that reported data on the accuracy of screening strategies for detecting UCDs. All included very small numbers with UCDs and were subject to partial verification bias, as those who tested negative did not undergo a reference standard. This means that these studies cannot reliably estimate sensitivity and specificity.

Therefore, commissioning an evidence summary on this question for any UCD at present is not justified, as it is unlikely that the findings would be substantially different to this evidence map.

Question 3: What is the volume and type of evidence available on the benefits and/or harms of interventions in asymptomatic and/or presymptomatic children with UCDs identified through screening?

Seven retrospective observational studies were included for this question (Table 4 and Appendix 2).⁴⁰⁻⁴⁶ Six used a comparative design and 1 was a single arm study. The studies each focused on a subset of between 1 and 5 specific UCDs (ARG1, ASS1, ASL, CPS1 or OTC). All studies reported on morbidity, mainly neurodevelopmental outcomes, and 2 also reported on mortality. No studies were identified which evaluated other outcomes of interest, such as patient quality of life, or potential harms from early treatment following screening.

The 6 comparative studies enrolled groups of newborns or children diagnosed with specific UCDs. They retrospectively compared outcomes in those identified through newborn screening and managed accordingly to outcomes in those diagnosed clinically after presenting with symptoms and managed accordingly.⁴⁰⁻⁴⁵ Five studies identified cases through population level newborn screening; 1 study screened family members of individuals affected with UCDs.⁴⁰ Most studies did not clearly describe how UCDs were managed in either group; 2 reported the use of dietary interventions and/or nitrogen scavenger therapy, others did not provide further detail.^{40,}

⁴¹ Studies were small (range of 42 to 109 participants, with 10 to 38 participants identified through newborn screening) which limits both their statistical power and generalisability and reflects the rarity of these conditions. One study was conducted in the UK. However, this study had a particularly small sample size (56 participants, of which only 10 were identified with a UCD through targeted screening).⁴⁰ The other studies were conducted in Taiwan, USA, Spain and multiple countries (not including the UK).

Four study abstracts reported better outcomes in cases detected through newborn screening compared with clinically diagnosed cases,⁴¹⁻⁴⁴ one reported improved short term metabolic outcomes but no difference in the number of long term hyperammonemic episodes,⁴⁵ and one reported no clear difference in outcomes.⁴⁰ However, the strength of evidence for these differences was unclear from the study abstracts and is unlikely to be strong given that all studies were very small. Additionally, it is likely that observed differences are due to differences in case-mix, with screen-detected cases including more good prognosis cases than the group that presents clinically.

The single arm study reported outcomes following treatment by dietary intervention in 6 children with CPS1 deficiency identified from a total of over 4 million newborns screened.⁴⁶ The very small number of cases and lack of a comparative group of clinically diagnosed cases mean it is not possible to determine how outcomes differ by mode or timing of diagnosis and subsequent intervention.

Table 4: Overview of 7 studies included for question 3

Study	Country	UCD	Screen detected UCDs	Symptom detected UCDs	Total UCD cases	Outcome types
Baruteau et al., 2017 ⁴⁰	UK	ASL	10	46	56	Morbidity (neurodevelopmental, metabolic)

Study	Country	UCD	Screen detected UCDs	Symptom detected UCDs	Total UCD cases	Outcome types
Chen et al., 2023 ⁴¹	Taiwan	CIT2	15	27	42	Morbidity (metabolic)
Landau et al., 2017 ⁴²	US	ARG1	0	3	50	Mortality, morbidity (neurodevelopmental)
		ASS1	5	6		
		ASL	5	8		
		CPS1	0	4		
		OTC	0	19		
Martin-Hernandez et al., 2025 ⁴³	Spain	ARG1	2	26	74*	Mortality, morbidity (neurodevelopmental)
		ASS1	18	14		
		ASL	7	7		
Posset et al., 2019 ⁴⁴	Multiple (Europe, Canada, US)	ASL	23	33	105	Morbidity (neurodevelopment)
		ASS1	15	34		
Posset et al., 2020 ⁴⁵	Multiple (Europe)	ASS1 or ASL**	51	58	109	Morbidity (metabolic)
Zhang et al., 2023 ⁴⁶	China	CPS1	6	Not applicable (single arm study)	6	Morbidity (neurodevelopmental)

* The reporting of clinically detected cases in this study was not transparent, data was extracted from number of cases diagnosed between 2014 and 2023.

** The number of cases with ASL or ASS1 was not reported separately.

In summary, the volume of evidence on the benefits and/or harms of interventions in asymptomatic and/or presymptomatic children with UCDs identified through screening is limited.

We identified 6 retrospective comparative studies and 1 retrospective single arm study that attempted to assess impact of interventions in asymptomatic and/or presymptomatic children with UCDs identified through screening; none reported data on harm. Most suggested better outcomes in cases detected through newborn screening compared with clinically diagnosed cases. However, all studies were very small. In addition, variations in conditions considered and outcomes measured means that in depth evidence synthesis would be unlikely to be conclusive. Therefore, commissioning an evidence summary on this question for any UCD is not justified, as it is unlikely that the findings would be significantly different to this evidence map.

Conclusions

We identified very little evidence for each of our 3 research questions. Only 2 documents reported recommendations based on expert panel consensus about newborn screening for UCDs. 6 studies reported on the accuracy of newborn screening strategies for specific UCDs, but the findings are likely to be subject to partial verification bias. We identified 6 retrospective comparative studies and 1 retrospective single arm study that attempted to assess the impact of interventions in asymptomatic and/or presymptomatic children with UCDs identified through screening; none reported data on harm. Most study abstracts reported differences in outcomes between screen-detected and clinically diagnosed cases, but the strength of the evidence was unclear and is unlikely to be strong due to small sample sizes. Furthermore, cases detected through newborn screening may be less severe and therefore not entirely comparable to cases diagnosed clinically after symptomatic presentation.

Larger prospective studies to evaluate patient outcomes following screening (in particular, the potential harms of interventions in individuals identified through screening) are needed. Accuracy studies should take steps to avoid partial verification bias, allowing more reliable estimates of sensitivity and specificity to be calculated: for example, by performing reference standard testing in a sufficiently large random sample of test-negative patients.

Recommendations

On the basis of this evidence map, the volume and type of evidence related to newborn screening for UCDs is currently unlikely to give a reliable estimate of the effectiveness of screening. Therefore, conducting a more detailed evidence review at this point is not justified.

Appendix 1 — Search strategies

MEDLINE Search

Database, version and platform

MEDLINE(R) ALL 1946 to April 21, 2025 via OvidSP.

Search date: 23 April 2025

#	Search terms	Hits
1	("urea cycle disorder\$" or "urea cycle defect\$" or "UCDs" or "PUCDs" or "urea cycle metabolism disorder\$" or "cytosolic UCDs" or "mitochondrial UCDs" or "proximal UCDs" or "distal UCDs").ti,ab,kw.	1419
2	((("Carbamoylphosphate synthetase I" or "Carbamoylphosphate synthetase 1" or "Carbamoyl-phosphate synthetase I" or "Carbamoyl-phosphate synthetase 1" or "Carbamoylphosphate synthetase" or "Carbamoyl-phosphate synthetase" or "Carbamoyl phosphate synthetase 1" or "Carbamoyl phosphate synthetase I" or "CPS1" or "CPSI") adj1 deficien\$).ti,ab,kw.	91
3	((("Ornithine transcarbamylase" or "Ornithine carbamoyltransferase" or "OTC" or "OCT") adj1 deficien\$).ti,ab,kw.	1068
4	((("N-acetyl glutamate synthetase" or "N-acetylglutamate synthase" or "NAGS") adj1 deficien\$).ti,ab,kw.	77
5	((("Argininosuccinic acid synthetase" or "Argininosuccinic acid synthase" or "Argininosuccinate synthetase" or "Argininosuccinate synthase" or "ASS" or "ASS1" or "ASSI") adj1 deficien\$).ti,ab,kw.	158
6	(Citrullinemia or "Citrullinemia type I" or "Citrullinemia type 1" or "CTLN1" or "CTLNI" or "citrin deficien\$" or "NICCD").ti,ab,kw.	750
7	((("Argininosuccinic acid lyase" or "Argininosuccinic lyase" or "Argininosuccinate lyase" or "Argininosuccinase" or "Argininosuccinatelyase" or "ASL" or "ASA") adj1 deficien\$).ti,ab,kw.	250
8	"Argininosuccinic aciduria".ti,ab,kw.	205
9	((Arginase or "Arginase 1" or "Arginase I" or "Arginase-1" or "Arginase-I" or "ARG1" or "ARGI") adj1 deficien\$).ti,ab,kw.	193
10	(Argininemia or Hyperargininemia).ti,ab,kw.	217
11	("CPS1D" or "CPSID" or "OTCD" or "ArgD" or "NAGSD" or "ASLD").ti,ab,kw.	396
12	"Urea Cycle Disorders, Inborn"/ or "Carbamoyl-Phosphate Synthase I Deficiency Disease"/ or "Ornithine Carbamoyltransferase Deficiency Disease"/ or Citrullinemia/ or "Argininosuccinic Aciduria"/ or Hyperargininemia/	2150
13	or/1-12	4073
14	(exp animals/ not humans.sh.)	5329623
15	13 not 14	3742
16	english.lg.	33840800
17	15 and 16	3419
18	limit 17 to yr="2015-2025"	1359

Embase Search

Database, version and platform

Embase 1974 to April 21, 2025 via OvidSP.

Search date: 23 April 2025

#	Search terms	Hits
1	("urea cycle disorder\$" or "urea cycle defect\$" or "UCDs" or "PUCDs" or "urea cycle metabolism disorder\$" or "cytosolic UCDs" or "mitochondrial UCDs" or "proximal UCDs" or "distal UCDs").ti,ab,kw.	2478
2	((("Carbamoylphosphate synthetase I" or "Carbamoylphosphate synthetase 1" or "Carbamoyl-phosphate synthetase I" or "Carbamoyl-phosphate synthetase 1" or "Carbamoylphosphate synthetase" or "Carbamoyl-phosphate synthetase" or "Carbamoyl phosphate synthetase 1" or "Carbamoyl phosphate synthetase I" or "CPS1" or "CPSI") adj1 deficien\$).ti,ab,kw.	157
3	((("Ornithine transcarbamylase" or "Ornithine carbamoyltransferase" or "OTC" or "OCT") adj1 deficien\$).ti,ab,kw.	1564
4	((("N-acetyl glutamate synthetase" or "N-acetylglutamate synthase" or "NAGS") adj1 deficien\$).ti,ab,kw.	125
5	((("Argininosuccinic acid synthetase" or "Argininosuccinic acid synthase" or "Argininosuccinate synthetase" or "Argininosuccinate synthase" or "ASS" or "ASS1" or "ASSI") adj1 deficien\$).ti,ab,kw.	266
6	(Citrullinemia or "Citrullinemia type I" or "Citrullinemia type 1" or "CTLN1" or "CTLNI" or "citrin deficien\$" or "NICCD").ti,ab,kw.	1114
7	((("Argininosuccinic acid lyase" or "Argininosuccinic lyase" or "Argininosuccinate lyase" or "Argininosuccinase" or "Argininosuccinatelyase" or "ASL" or "ASA") adj1 deficien\$).ti,ab,kw.	349
8	"Argininosuccinic aciduria".ti,ab,kw.	295
9	((Arginase or "Arginase 1" or "Arginase I" or "Arginase-1" or "Arginase-I" or "ARG1" or "ARGI") adj1 deficien\$).ti,ab,kw.	297
10	(Argininemia or Hyperargininemia).ti,ab,kw.	303
11	("CPS1D" or "CPSID" or "OTCD" or "ArgD" or "NAGSD" or "ASLD").ti,ab,kw	573
12	urea cycle disorder/ or argininosuccinic aciduria/ or exp citrullinemia/ or exp citrin deficiency/ or ornithine transcarbamylase deficiency/ or carbamoyl phosphate synthetase I deficiency/ or hyperargininemia/ or hyperornithinemia/ or hyperornithinemia hyperammonemia homocitrullinuria syndrome/ or NAGS deficiency/	4640
13	or/1-12	6748
14	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset\$1).ti. and animal experiment/	1296945
15	Animal experiment/ not (human experiment/ or human/)	2734162
16	14 or 15	2815113
17	13 not 16	6333
18	english.lg.	38232696
19	17 and 18	5920
20	(Conference Abstract or Conference Paper).pt.	6226005

#	Search terms	Hits
21	19 not 20	4246
22	limit 21 to yr="2015-2025"	1883

Additional sources

The search results were initially sifted by the information specialist using a sensitive approach, only excluding reports which were obviously irrelevant, published prior to 2015, or were not written in English language. Relevant publications were checked against those already identified through the MEDLINE and Embase search results to remove duplicate results prior to screening.

Searching the following additional sources identified 86 references which were screened in addition to the main search

Orphanet website (search conducted on 30 April 2025)

The search consisted of individual searches for each of the urea cycle disorder conditions (using the official Orphanet heading term) listed below. Each condition search term was entered into the search box on the 'search for a rare disease' page at <https://www.orpha.net/en/disease>:

1. Carbamoyl-phosphate synthetase 1 deficiency
2. Ornithine transcarbamylase deficiency
3. Hyperammonemia due to N-acetylglutamate synthase deficiency
4. Citrullinemia type I (Argininosuccinate synthase deficiency)
5. Acute neonatal citrullinemia type I
6. Late-onset citrullinemia type I
7. Citrullinemia type II
8. Argininosuccinic aciduria (Argininosuccinic acid lyase)
9. Argininemia (Arginase 1)

Search results in the categories 'guidelines' and 'review articles' were examined. The focus was on identifying guidelines or guidance documents (including all types, not just those focused on screening). Publications from 2015 onwards and in English were manually filtered, as no search date limit was specified in the search box. The search retrieved 24 relevant references.

Orphanet Newborn Screening Bibliographical Knowledgebase (search conducted on 6 May 2025)

The search consisted of individual searches for each of the ORPHAcodes related to UCD conditions on the search page at <https://nbs.orphanet.app/?lang=en>:

1. ORPHA:147 (Carbamoyl-phosphate synthetase 1 deficiency)
2. ORPHA:664 (Ornithine transcarbamylase deficiency)

3. ORPHA:927 (Hyperammonemia due to N-acetylglutamate synthase deficiency)
4. ORPHA:247525 (Citrullinemia type I (Argininosuccinate synthase deficiency))
5. ORPHA:247546 (Acute neonatal citrullinemia type I)
6. ORPHA:247573 (Late-onset citrullinemia type I)
7. ORPHA:247585 (Citrullinemia type II)
8. ORPHA:23 Argininosuccinic aciduria (Argininosuccinic acid lyase))
9. ORPHA:90 (Argininemia (Arginase 1))

The search retrieved 15 relevant references.

Google (search conducted on 8 May 2025)

The following search terms and limits were entered into the Google Advanced Search page at https://www.google.co.uk/advanced_search:

1. "Urea Cycle Disorders" in the 'this exact word or phrase' box
2. guideline, guidelines, guidance, recommendation, recommendations, screening in the 'any of these words' box
3. English language filter applied using the 'narrow your results by language' box

Sifting was halted when the last 2 pages contained no relevant results. This resulted in 13 pages being screened, of which 130 results retrieved 47 relevant references or links.

Inclusions and Exclusions

Evidence for all questions was restricted to full reports available in English reported from the 1 January 2015 to May 2025. Conference abstracts, commentaries and editorials were not included. Systematic reviews were eligible for all questions and were treated as a source of eligible studies. Studies from identified systematic reviews were included individually if they met the criteria below.

Question 1: Are there any national or international guidelines or recommendations on newborn screening for UCDs?

Current national and/or international guidelines/recommendations on diagnosis and/or management of newborn screening for UCDs were eligible.

Question 2: What is the volume and type of evidence on the accuracy of newborn screening strategies for UCDs using dried blood spots?

Population	Newborns
Index test	Any standalone test or any series of sequential tests or combination of parallel tests used to screen for UCDs using dried blood spots

Reference standard	Any reported reference standard
Target condition	Any UCD, including mitochondrial UCDs (OTC, CPS1 and NAGS deficiencies), cytosolic UCDs (ASS1, ASL and ARG1 deficiencies) and secondary UCDs (ORNT1 and citrin deficiencies)
Outcomes	Any measure of accuracy (e.g. sensitivity, specificity, positive predictive values, negative predictive values, likelihood ratios)
Study designs	One gate or two gate test accuracy studies

Question 3: What is the volume and type of evidence available on the benefits and/or harms of interventions in asymptomatic and/or presymptomatic children with UCDs identified through screening?

Population	<p>Study design-specific criteria:</p> <p><i>Comparative interventional studies:</i> Newborns (for population screening studies) or newborns with an affected family member (for targeted screening or cascade testing studies)</p> <p><i>Comparative observational and single arm treatment studies:</i> Individuals with UCDs</p>
Interventions	<p>Study design-specific criteria:</p> <p><i>Comparative interventional studies:</i> Population screening, targeted screening, or cascade testing followed by treatment (e.g. dialysis, nitrogen scavenger therapy, dietary interventions, liver transplantation) of affected individuals</p> <p><i>Comparative observational studies and single arm studies:</i> Any reported treatment (e.g. dialysis, nitrogen scavenger therapy, dietary interventions, liver transplantation), where treatment is administered at an early, pre-symptomatic stage (e.g. through population screening or cascade testing)</p>
Comparator	<p>Study design-specific criteria:</p> <p><i>Comparative interventional studies:</i> No screening; treatment (e.g. dialysis, nitrogen scavenger therapy, dietary interventions, liver transplantation) of affected individuals following symptomatic presentation</p> <p><i>Comparative observational studies:</i> Intervention treatment, administered following symptomatic presentation or no treatment (natural history)</p> <p><i>Single arm treatment studies:</i> Not applicable (no comparator)</p>
Outcomes	Any patient perceived outcome (e.g. morbidity and mortality associated with UCDs, quality of life, harms of treatments)
Study designs	<p>Comparative interventional studies (e.g. RCTs, cluster RCTs, non-randomised studies of interventions (NRSI))</p> <p>Comparative observational studies (e.g. cohort studies, case-control studies)</p> <p>Single arm treatment studies</p>

Appendix 2 – Abstract reporting

Question 1: Are there any national or international guidelines or recommendations on newborn screening for UCDs?

Citation 1: Burlina et al (2023)³⁰

Study type: National guidelines

Objectives: Italian national expert panel consensus recommendations relating to screening for and the diagnosis, treatment, and follow-up of UCDs.

Issuing body: Expert panel comprised of 6 metabolic paediatricians from Italian paediatric, metabolic and rare diseases centres, with expertise in managing and treating UCDs, as well as 2 biochemists experts in biochemical and genetic confirmation of newborn screening-positive results.

Conclusions: Recommends newborn screening for all UCDs.

Citation 2: Haberle et al (2019)²⁹

Study type: National guidelines

Objectives: Israeli and European international expert panel consensus recommendations relating to screening for and the diagnosis, treatment, and follow-up of UCDs.

Issuing body: Expert panel which included 10 paediatric metabolic specialists, a paediatric nephrologist, a metabolic specialist for adults, a medical biochemist, a psychologist, and a metabolic dietitian.

Conclusions: Recommends newborn screening for ASL and ASS1 only, citing insufficient published evidence for screening other UCDs such as NAGS, CPS1D, OTC, and ARG1 .

Citation 3: ACMG (2022)³¹

Study type: National guidelines

Objectives: US national guidelines for management of ARG1 after a positive newborn screening result.

Issuing body: American College of Medical Genetics.

Conclusions: Not applicable, practical guidelines.

Citation 4: ACMG (2022)³²

Study type: National guidelines

Objectives: US national guidelines for management of ASS1, ASL and CIT2 after a positive newborn screening result.

Issuing body: American College of Medical Genetics.

Conclusions: Not applicable, practical guidelines.

Citation 5: ACMG (2021)³³

Study type: National guidelines

Objectives: US national guidelines for management of OTC, CPS1 and NAGS after a positive newborn screening result.

Issuing body: American College of Medical Genetics (ACMG)

Conclusions: Not applicable, practical guideline

Question 2: What is the volume and type of evidence on the accuracy of newborn screening strategies for UCDs using dried blood spots?

Citation 1: Belaramani et al (2024)³⁴

Study type: One gate

Objectives: Evaluation of newborn screening programme for inborn errors of metabolism in Hong Kong, between 2015 and 2022.

Components of the study:

Size: 125,688

Country: Hong Kong

Index test: Tandem-MS

Reference standard: Genetic testing in index positives only. Clinical diagnosis in those that tested negative and later presented with symptoms.

Outcomes reported: The full text reported PPV for CIT2 (14.3%)

Conclusions: No conclusions related to the accuracy of tests reported in the abstract. The full text reported PPV for CIT2.

Citation 2: Chen et al (2022)³⁵

Study type: One gate

Objectives: To evaluate the addition of second tier newborn screening testing for CIT2 implemented after 2018.

Components of the study:

Size: 753,520

Country: Taiwan

Index test: Genetic and tandem-MS

Reference standard: Unclear but applied to index positives only. Clinical diagnosis in those that tested negative and later presented with symptoms.

Outcomes reported: The full text reported that PPV was higher after the addition of second tier testing for CIT2 but did not report the actual value

Conclusions: No conclusions related to the accuracy of tests reported in the abstract. The full text reported PPV for OTC. Test positivity was reported for ASL, ASS1, CIT2 and CPS1 .

Citation 3: Lam et al (2020)³⁶

Study type: One gate

Objectives: To evaluate an 18-month pilot study of inborn errors of metabolism in Hong Kong, which included CIT2.

Components of the study:

Size: 15,138

Country: Hong Kong

Index test: Tandem-MS

Reference standard: Genetic testing in index positives only. Clinical diagnosis in those that tested negative and later presented with symptoms.

Outcomes reported: The full text reported test positivity from which PPV could be calculated for CIT 2. The number of known false negatives was also reported; therefore, sensitivity and specificity could also be calculated but may be biased due to under-ascertainment.

Conclusions: No conclusions related to the accuracy of tests reported in the abstract. The full text reported test positivity and false negatives from which PPV could be calculated for CIT2.

Citation 4: Lund et al (2020)³⁷

Study type: One gate

Objectives: To evaluate a newborn screening programme for inborn errors of metabolism conducted between 2002 and 2019 in Denmark.

Components of the study:

Size: 967,780

Country: Denmark

Index test: Tandem-MS

Reference test: Biochemical and genetic testing in index positives only. Clinical diagnosis in those that tested negative and later presented with symptoms.

Outcomes reported: The abstract reported PPV for the entire screening cohort. The full text reported test positivity from which PPV could be calculated for ARG1, ASL and ASS1. The number of known false negatives was also reported; therefore, sensitivity and specificity could also be calculated but may be biased due to under-ascertainment.

Conclusions: The abstract reported PPV for the entire screening cohort. The full text reported test positivity and false negatives from which PPV could be calculated for ARG1, ASL and ASS1.

Citation 5: Maier et al (2023)³⁸

Study type: One gate

Objectives: To evaluate 18 candidate diseases for potential inclusion in a German newborn screening programme, including ASS1 and CIT2.

Components of the study:

Size: 1.77 million

Country: Germany

Index test: Tandem-MS

Reference standard: Biochemical and genetic testing in index positives only. Clinical diagnosis in those that tested negative and later presented with symptoms.

Outcomes reported: The abstract reported PPV for the entire screening cohort. The full text reported PPV for ASS1 (43%)

Conclusions: The abstract reported PPV for the entire screening cohort. The full text reported PPV for ASS1 and CIT2 .

Citation 6: Staretz-Chacham et al (2021)³⁹

Study type: One gate

Objectives: To evaluate whether incorporating orotic acid measurement into routine newborn screening improves detection of UCDs.

Components of the study:

Size: 1.15 million

Country: Israel

Index test: Biochemical

Reference standard: Genetic testing in index positives only. Clinical diagnosis in those that tested negative and later presented with symptoms.

Outcomes reported: The full text reported PPV (12.72%), sensitivity (63.63%), and specificity (99.99%) for OTC, as well as test positivity for ASL, ASS1, CIT2 and CPS1.

Conclusions: No conclusions related to the accuracy of tests reported in the abstract.

Question 3: What is the volume and type of evidence available on the benefits and/or harms of interventions in asymptomatic and/or presymptomatic children with UCDs identified through screening?

Citation 1: Baruteau et al (2017)⁴⁰

Study type: Retrospective study

Objectives: Outcomes of children and newborns with ASL in a UK cohort, comparing patients identified clinically or through newborn screening.

Components of the study:

Size: 56

Country: UK

Intervention: Screen detection of UCD followed by clinical management (nitrogen scavenger therapy and dietary modifications)

Comparator: Symptomatic diagnosis of UCD followed by clinical management (nitrogen scavenger therapy and dietary modifications)

Outcomes reported: Morbidity (neurodevelopmental and metabolic outcomes)

Conclusions: No clear difference in outcomes in cases identified through screening compared to patients diagnosed clinically after symptom presentation.

Citation 2: Chen et al (2023)⁴¹

Study type: Retrospective study

Objectives: To compare clinical outcomes between CIT2 patients identified through newborn screening and those diagnosed later due to symptomatic cholestasis or hepatitis.

Components of the study:

Size: 42

Country: Taiwan

Intervention: Screen detection of UCD followed by clinical management (dietary modifications)

Comparator: Symptomatic diagnosis of UCD followed by clinical management (dietary modifications)

Outcomes reported: Morbidity (metabolic outcomes)

Conclusions: Abstract reports that patients identified early by newborn screening had better prognosis, however statistical analysis reported in full text report shows no clear difference in mortality, failure to thrive and metabolic outcomes.

Citation 3: Landau et al (2017)⁴²

Study type: Retrospective study

Objectives: To assess long-term clinical and neurodevelopmental outcomes of metabolic disorders identified by expanded newborn screening compared to those diagnosed clinically at Boston Children's Hospital.

Components of the study:

Size: 50

Country: US

Intervention: Screen detection of UCD followed by clinical management (unclear)

Comparator: Symptomatic diagnosis of UCD followed by clinical management (unclear)

Outcomes reported: Mortality, morbidity (neurodevelopmental outcomes)

Conclusions: Abstract reported that there was substantial improvement in the overall metabolic outcomes of newborns identified through screening, however the outcomes are combined across several metabolic conditions (not specific to UCDs).

Citation 4: Martin-Hernandez et al (2025)⁴³

Study type: Retrospective study

Objectives: To update the Spanish UCD registry and evaluate how newborn screening and current therapies influence clinical outcomes in patients with urea cycle disorders (including ARG1, ASS1 and ASL).

Components of the study:

Size: 74

Country: Spain

Intervention: Screen detection of UCD followed by clinical management (unclear)

Comparator: Symptomatic diagnosis of UCD followed by clinical management (unclear)

Outcomes reported: Mortality and morbidity (neurodevelopmental outcomes)

Conclusions: Abstract and full text reported positive impact of newborn screening detection on patient mortality and neurodevelopmental outcomes.

Citation 5: Posset et al (2019)⁴⁴

Study type: Retrospective study

Objectives: To evaluate how diagnostic timing and therapeutic strategies influence cognitive outcomes in individuals with UCDs

Components of the study:

Size: 105

Country: Multiple, (Europe, Canada, US)

Intervention: Screen detection of UCD followed by clinical management (liver transplantation and nitrogen scavenger therapy)

Comparator: Symptomatic diagnosis of UCD followed by clinical management (liver transplantation and nitrogen scavenger therapy)

Outcomes reported: Morbidity (neurodevelopment outcomes)

Conclusions: Abstract and full text reported improved neurodevelopmental outcomes in the screen detected group compared to the clinically detected patients.

Citation 6: Posset et al (2020)⁴⁵

Study type: Retrospective study

Objectives: To assess the impact of newborn screening on the metabolic disease course and outcomes in individuals with ASS1 and ASL, accounting for disease severity.

Components of the study:

Size: 109

Country: Multiple (Europe)

Intervention: Screen detection of UCD followed by clinical management (unclear)

Comparator: Symptomatic diagnosis of UCD followed by clinical management (unclear)

Outcomes reported: Morbidity (metabolic outcomes)

Conclusions: Abstract and full text reported improved short term metabolic outcomes but no clear difference in long term hyperammonemic episodes in screen detected compared to clinically detected patient group when adjusted for severity of symptoms.

Citation 7: Zhang et al (2023)⁴⁶

Study type: Retrospective study

Objectives: To investigate the genotype-phenotype characteristics and long-term prognosis of CPS1 deficiency in children detected through newborn screening in Zhejiang province.

Components of the study:

Size: 6

Country: China

Intervention: Screen detection of UCD followed by clinical management (dietary)

Comparator: Not applicable, single arm study

Outcomes reported: Morbidity (neurodevelopmental outcomes)

Conclusions: There was no comparison group, however the abstract reported that early identification can improve prognosis. Of the 6 newborns followed up for between 9 months to 10 years, 3 experienced hyperammonemia, 1 had attention deficit hyperactivity disorder, 1 had transient facial twitching, 1 had increased muscle tone and 1 patient died. The 5 surviving patients had normal scores of the Ages & Stages Questionnaires and Griffiths Development Scales.

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