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

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1 Plain English Summary

1.1 What is the problem?

Urea cycle disorders (UCDs) are rare inherited conditions where the body cannot properly dispose of waste nitrogen produced when digesting protein. This happens because one of the important enzymes needed for this waste disposal is missing or does not work well. This means harmful levels of ammonia can build up in the body. This can cause symptoms like being sick, not wanting to eat, and feeling very tired, within days of birth. If UCDs are not treated, symptoms can rapidly worsen and lead to serious problems like brain swelling, coma, or even death. How quickly symptoms appear and how severe they are depends on which enzyme is affected and how much of it is missing. UCDs are rare, affecting about 1 in every 52,000 babies.

Treatments can involve medications, special diets, or filtering the blood. During a serious episode (called a crisis), it is important to lower ammonia levels in the blood very quickly. Sometimes, a liver transplant is needed to help the body manage ammonia better. Although a transplant will not fix brain damage that has already happened, it can prevent future problems and reduce the need for ongoing treatment.

The need for long-term care reflects the severity of the condition. Some people only need to be careful when sick or having surgery. Others need to stay on a low-protein diet and take medicine for life. Some with development disabilities may require additional support.

1.2 What are we trying to find out?

The UK National Screening Committee wants to find out whether testing all newborn babies for UCDs (screening) would help babies and their families. As a first step, they need to check if there is enough reliable evidence to support exploring the topic in more depth.

We're looking at:

- Whether other countries already screen for UCDs or have guidelines in place
- How many studies and what type of studies have looked at how well current tests work – how good are they at detecting UCDs in newborns and not wrongly identifying babies who do not have UCDs?
- How many studies and what type of studies have looked at whether early diagnosis and treatment through screening leads to better health outcomes

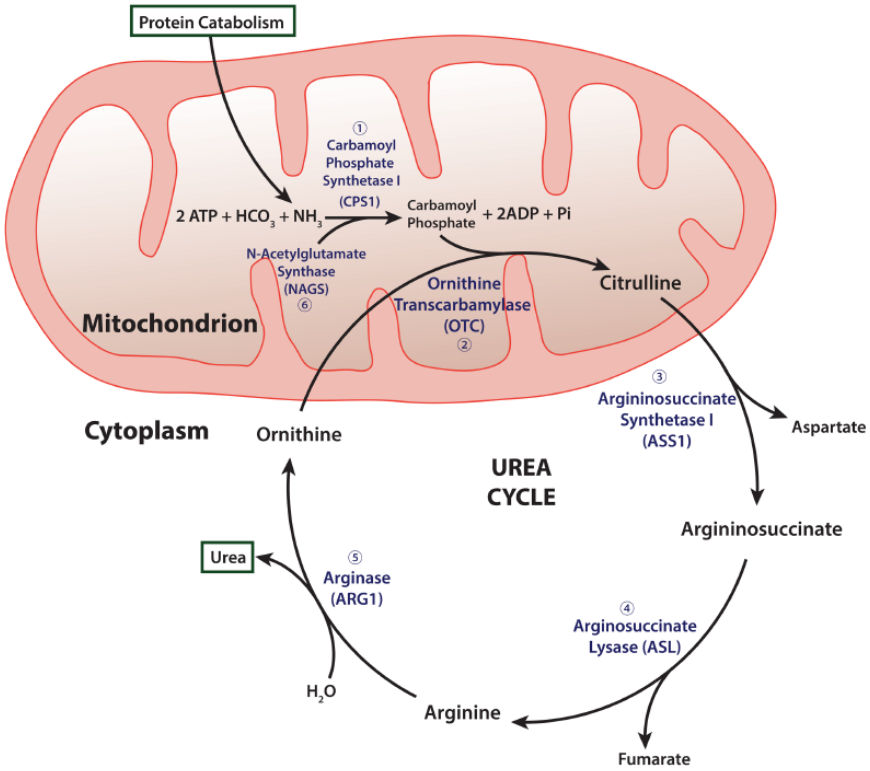
2 Background

2.1 Urea cycle disorders (UCD)

Urea Cycle Disorders (UCD) are a group of inherited metabolic conditions caused by a deficiency of one of the main six enzymes in the urea cycle. Two additional secondary urea cycle disorders are also recognised in the literature, and these are due to inherited deficiencies of two amino acid transporters also involved in the urea cycle: ornithine translocase (ORNT1: ornithine/citrulline carrier) and citrin (aspartate/glutamate carrier).[1]

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,[1, 2] (see Figure 1). The urea cycle is also the sole source of endogenous production of the amino acids arginine, ornithine and citrulline.[1] The cumulative incidence of all urea cycle disorders has been estimated as 1 in 35,000 live births,[3] although more recent studies have estimated a lower cumulative incidence of around 1 in 51,946 live births.[4]

Figure 1 Outline of the urea cycle which produces urea as part of protein metabolism. The six enzymes involved in the pathway are numbered 1–6, with their associated gene in brackets. Source: Blair et al. 2014[2]



The main six 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)
- Argininosuccinic acid lyase (ASL, also known as argininosuccinic aciduria)
- Arginase (ARG1, also known as argininemia)

2.2 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.[5, 6] 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 asymptomatic, though they can show considerable variation in clinical symptoms, including debilitating and life-threatening hyperammonaemia.[2, 5]

Severe deficiency or total absence of any of the first four 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 vomiting, anorexia and lethargy which rapidly progresses to encephalopathy, coma and death if untreated.[1, 7] 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 neonatal 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, holidays, peripartum period).[1]

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.[5]

2.3 Diagnosis of UCDs

Newborn screening requires the presence of a suitable marker to indicate the 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.[8] 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.[1, 5, 7] 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.[8] Molecular genetic testing is the primary method of diagnostic confirmation for all UCDs.[1, 5, 7]

2.4 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.[1, 5, 7, 9] 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.[9] 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.[5]

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.[10] 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.[11]

2.5 Current guidance on screening for UCDs

Newborn screening for UCDs is not widespread. This is, in part, because there is a concern that often, especially in severely manifesting mitochondrial UCDs, the symptoms are severe and dangerous hyperammonaemia often manifests within a few days after birth.[7, 8] 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.[7, 8] When it occurs, newborn screening tends to include only the cytosolic UCDs. Currently, newborn screening for a selection of UCDs takes place in some states in the United States (US), in Australia and some countries in Europe such as Italy, Portugal, Poland and Sweden.[8, 9, 12] Screening for ASL deficiency also took place in Austria between 1973 and 2000 but there were concerns that several of the identified cases had partial deficiency which even untreated might have never come to medical attention.[13]

In 2012 Häberle et al. published guidelines for the diagnosis and management of UCDs. These have been updated in 2019.[7] In relation to newborn screening, Häberle et al recommend considering the possibility of newborn screening for ASS1

deficiency and ASL deficiency but note that there is insufficient evidence for a recommendation on newborn screening programmes for the mitochondrial UCDs and for ARG1 deficiency.[7]

In 2015, the Royal College of Paediatric and Child Health (RCPCH) published a clinical guideline for the management of children and young people with an acute decrease in conscious level. 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.[14]

Metabolic Support UK had 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.[15]

2.6 Rationale and Previous review on newborn screening for UCDs

The UK National Screening Committee (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 (https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process).

The UK NSC does not currently recommend screening for any UCDs. In 2015, the UK NSC commissioned a review which focused exclusively on screening for citrullinaemia (ASS1 deficiency) and 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.[16]

The open call for new screening topics was introduced as part of the UK NSC's evidence review process to ensure stakeholders have a regular opportunity to suggest new topics for evaluation against the UK NSC remit and criteria. As part of the 2022 open call for topics, a submission was made to screen newborns for UCDs, specifically for ornithine transcarbamylase (OTC) deficiency. The proposal was considered by an evaluation group which included the UK NSC chair, the chairs of the UK NSC's Fetal, Maternal and Child Health group and Adult Reference Group, patient and public voice (PPV) 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.

This is the first time that screening for all UCDs has been considered by the UK NSC, therefore, a preliminary evidence map to evaluate the amount of evidence related to screening for this group of conditions may help determine if further work is required.

An evidence map is a rapid evidence product which aims to gauge the volume and type of evidence relating to a specific topic. A systematic literature search is undertaken, and titles and abstracts are sifted to identify the relevant literature. For some references, the full text may be reviewed for clarity. The relevant evidence is then summarised, and a recommendation made on whether the evidence is sufficient to justify a more in-depth evidence summary or whether the topic should be re-considered in 3 years.

3 Aims of the evidence map

Newborn blood spot (NBS) screening for UCDs has not previously been assessed by the UK NSC. This evidence map will provide a summary of the volume and type of evidence to inform three key questions relating to NBS screening for UCDs:

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 presymptomatic/asymptomatic children with UCDs identified through screening? i.e. does early initiation of treatment following screening provide better outcomes for UCDs compared with initiation of treatment following clinical detection?

This evidence map will inform consideration, by the UK NSC, of whether further work on this topic is currently justified.

4 Methods for the evidence map

An evidence map will be prepared, in accordance with UK NSC process guidance.[17] Studies will be assessed for inclusion and included articles will be reviewed at the abstract level, with full text articles examined only where key information is not clear from the abstract. Separate inclusion criteria have been developed for each key question.

4.1 Inclusion and exclusion criteria

Evidence for all questions will be restricted to full reports available in English reported in the past 10 years. Conference abstracts, commentaries and editorials will not be included. For questions 2 and 3, studies from the UK will be prioritised, but all identified studies will be reported. Systematic reviews will also be eligible for all questions and will be treated as a source of eligible studies. Studies from identified systematic reviews will be included individually if they meet the criteria below.

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

Any current national and/or international guidelines/recommendations on newborn screening for UCDs will be included. Details of any implemented national newborn

screening programmes for UCDs will also be provided, irrespective of whether related published guidelines are identified. Guidelines on diagnosis and/or management of UCDs will also be included.

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

Table 1 provides an overview of inclusion criteria for this question.

Table 1 Inclusion criteria for question 2

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

4.1.3 Question 3: What is the volume and type of evidence available on the benefits and/or harms of interventions in presymptomatic/asymptomatic children with UCDs identified through screening? i.e. does early initiation of treatment following screening provide better outcomes for UCDs compared with initiation of treatment following clinical detection?

Table 2 provides an overview of the inclusion criteria for this question; inclusion criteria are specified for each eligible study design.

Table 2 Inclusion criteria for question 3

Population	Study design-specific criteria: • *Comparative interventional studies:* Newborns (for population screening studies) or newborns with an affected family member (for targeted screening or cascade testing studies) • *Comparative observational and single arm treatment studies:* Individuals with UCDs
Interventions	Study design-specific criteria: • *Comparative interventional studies:* Population screening, targeted screening, or cascade testing followed by treatment (e.g. dialysis, nitrogen scavenger therapy, dietary interventions, liver transplantation) of affected individuals

	• *Comparative observational studies and single arm studies:* 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)
Comparator	Study design-specific criteria: • *Comparative interventional studies:* No population screening, targeted screening, or cascade testing; treatment (e.g. dialysis, nitrogen scavenger therapy, dietary interventions, liver transplantation) of affected individuals following symptomatic presentation • *Comparative observational studies:* Intervention treatment, administered following symptomatic presentation or no treatment (natural history) • *Single arm treatment studies:* Not applicable (no comparator)
Outcomes	Any patient perceived outcome (e.g. morbidity and mortality associated with UCDs, quality of life, harms of treatments)
Study designs	• Comparative interventional studies (e.g. RCTs, cluster RCTs, non-randomised studies of interventions (NRSI)) • Comparative observational studies (e.g. cohort studies, case-control studies) • Single arm treatment studies

4.2 Study identification

Studies will be identified using bibliographic and non-bibliographic search methods following the UK NSC guidelines for evidence maps.

4.2.1 Bibliographic searching

The following databases will be searched:

- MEDLINE (Ovid SP)
- EMBASE (Ovid SP)

A sensitive search strategy based on condition-related terms for each urea cycle disorder will be used. Search limits will be applied to exclude animal studies and to retrieve only English language studies (a criteria specified for this evidence map). Additionally, a publication type limit will be applied to the EMBASE search to exclude conference abstracts and conference papers. In order to maintain relevance to current clinical practice, a date limit to identify papers published between 2015 and 2025 will also be applied to the search. Draft search strategies for the MEDLINE and EMBASE databases are reported in the Appendix .

4.3 Non-bibliographic search methods

International guidelines will be identified through searches of the following:

- Orphanet via https://www.orpha.net/ and the Orphanet Newborn Screening Bibliographical Knowledge base via https://nbs.orphanet.app/?lang=en
- Google search (via https://www.google.com/) using a combination of terms for 'guidelines' or 'guidance' and 'urea cycle disorders' including terms for each of the different urea cycle disorders

Additional relevant studies will be identified by hand searching the websites of relevant international organisations/societies such as the International Society for Neonatal Screening.

4.3.1 Managing the searches

Search results will be exported to EndNote 21 for deduplication using the default deduplication settings and manual review of records. Search results will be imported into Nested Knowledge® (nested-knowledge.com) for screening.

4.4 Review strategy

Review processes will be undertaken in Nested Knowledge®, systematic review software.

All titles and abstracts identified by the searches will be screened by one reviewer. A random sample of 20% of records will be independently screened by a second reviewer with the remaining 80% second checked using “Robot Reviewer” the AI second reviewer in Nested Knowledge®. Where there is a disagreement between the first reviewer and second reviewer (human or AI), disagreements will be resolved through discussion. Full texts will be examined, as necessary, to clarify information which is unclear from the abstract.

Full data extraction and risk of bias assessment is not part of the evidence map process. The following 'top level’ information will be extracted from each included study:

- For review question 1: year of publication, type of guideline (national or international), country, issuing body, and purpose (screening, diagnosis, and / or management of UCD) of the guideline or recommendation, and key recommendations
- For review question 2: UCD targeted, objectives, index test evaluated, study design (one gate or two gate), reference standard, measure(s) of diagnostic accuracy reported, study location, conclusions,
- For review question 3: objectives, study design, location, number of participants (study size), age group (newborns or older), type of UCD studied, intervention, comparator (if applicable), patient perceived outcomes reported, conclusions

This simplified data extraction process will be undertaken by one reviewer and checked by a second reviewer.

4.5 Synthesis methods

A summary of the volume and type of available evidence will be provided for each key question. We will also provide an overview of the countries where screening is recommended. This summary will include an indication of whether the current evidence base is likely to be adequate to justify further assessment.

In addition, a brief description of each included study will be provided (based on the 'top level' data extraction described above). This study level information will also be summarised in tables and figures, which will be designed to facilitate rapid visualisation of the volume and type of available evidence.

5 Competing interests of authors

None of the authors have any competing interests.

6 Timetable/milestones

Tasks	Target dates
Start	1 April 2025
Protocol	15 April 2025
First evidence map draft	20 May 2025
BESS Group responding to the feedback from UK NSC Evidence team	3rd June
Reference group meeting	18 September 2025 Feedback from reference group to be sought ASAP once the draft is ready (via email if necessary) by the end of week 12 i.e. by Friday 20 June
ESGs responding to the feedback from reference group	Updated version to be ready 2 weeks (by week 14) after receiving feedback i.e. by 4 July
UK NSC meeting	27 November 2025 Feedback from UK NSC to be sought at earliest opportunity
ESGs responding to the feedback from the UK NSC	Final document to be ready ASAP after the UK NSC meeting

7 References

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Appendix: Literature search strategies

Draft Medline Search

Database, version and platform

MEDLINE(R) ALL 1946 to April 11, 2025 via OvidSP. Please note that this date (April 11, 2025) reflects the version of the database at the search development date and not the exact version of the database when the search will be conducted.

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

Draft EMBASE Search

Database, version and platform

Embase 1974 to April 11, 2025 via OvidSP.

Please note that this date (April 11, 2025) reflects the version of the database at the search development date and not the exact version of the database when the search will be conducted.

#	Search terms
1	("urea cycle disorder$" or "urea cycle defect$" or "UCDs" or "PUCDs" or "urea cycle metabolism disorder$" or "cytosolic UCDs" or "mitochondrial UCDs" or "proximal UCDs" or "distal UCDs").ti,ab,kw.
2	(("Carbamoylphosphate synthetase I" "Carbamoylphosphate synthetase 1" or "Carbamoyl-phosphate synthetase I" or "Carbamoyl-phosphate synthetase 1" or "Carbamoylphosphate synthetase" or "Carbamoyl-phosphate synthetase" or "Carbamoyl phosphate synthetase 1" or "Carbamoyl phosphate synthetase I" or "CPS1" or "CPSI") adj1 deficien$).ti,ab,kw.
3	(("Ornithine transcarbamylase" or "Ornithine carbamoyltransferase" or "OTC" or "OCT") adj1 deficien$).ti,ab,kw.
4	(("N-acetyl glutamate synthetase" or "N-acetylglutamate synthase" or "NAGS") adj1 deficien$).ti,ab,kw.
5	(("Argininosuccinic acid synthetase" or "Argininosuccinic acid synthase" or "Argininosuccinate synthetase" or "Argininosuccinate synthase" or "ASS" or "ASS1" or "ASSI") adj1 deficien$).ti,ab,kw.
6	(Citrullinemia or "Citrullinemia type I" or "Citrullinemia type 1" or "CTLN1" or "CTLNI" or "citrin deficien$" or "NICCD").ti,ab,kw.
7	(("Argininosuccinic acid lyase" or "Argininosuccinic lyase" or "Argininosuccinate lyase" or "Argininosuccinase" or "Argininosuccinatelyase" or "ASL" or "ASA") adj1 deficien$).ti,ab,kw.
8	"Argininosuccinic aciduria".ti,ab,kw.
9	((Arginase or "Arginase 1" or "Arginase I" or "Arginase-1" or "Arginase-I" or "ARG1" or "ARGI") adj1 deficien$).ti,ab,kw.
10	(Argininemia or Hyperargininemia).ti,ab,kw.
11	("CPS1D" or "CPSID" or "OTCD" or "ArgD" or "NAGSD" or "ASLD").ti,ab,kw
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/
13	or/1-12
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/
15	Animal experiment/ not (human experiment/ or human/)
16	14 or 15
17	13 not 16
18	english.lg.
19	17 and 18
20	(Conference Abstract or Conference Paper).pt.
21	19 not 20
22	limit 21 to yr="2015-2025"