National Institute for Health and Care Excellence

Consultation

Renal and ureteric stones: assessment and management

Metabolic investigations

NICE guideline

Intervention evidence review

July 2018

Consultation

This evidence review was developed by the National Guideline Centre

Disclaimer

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1.1 Review question: In people with renal or ureteric stones, what is the clinical and cost effectiveness of stone analysis, blood tests and urine tests compared to no test, when each is followed by the appropriate treatment for renal and ureteric stones, in order to improve patient outcomes?

1.2 Introduction

Laboratory testing can define a metabolic diagnosis in stone patients. Subsequent treatment can reduce the risk of recurrence of stones by modifying an individual's metabolic status accordingly. Certain stone subgroups such as uric acid stones and cystine stones have established therapeutic pathways. However, the therapeutic pathway for the largest subgroup, mixed calcium stones, is unclear. Due to the size of this population, this group of stones have the biggest implications in terms of health resources.

Laboratory testing for a metabolic abnormality can range from basic testing which includes a stone analysis only, to advanced testing including blood and urine tests. Current practice is varied and it is currently unclear which metabolic laboratory tests should be done and whether testing should be done for all people with a stone, or just those at high risk of developing a recurrent stone. PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People (adults, children and young people) with symptomatic and asymptomatic renal or ureteric stones

Index test + treatment	**Index tests:**
	• Stone analysis
	• Blood tests:
	  ○ calcium levels (for hypercalcaemia)
	  ○ uric acid levels (for hyper- or hypo- uricaemia)
	• Urine tests:
	  ○ calcium levels (for hypercalciuria)
	  ○ oxalate levels (for hyperoxaluria)
	  ○ uric acid levels (for hyper- or hypo- uricosuria)
	  ○ citrate level (for hypocitraturia)
	  ○ sodium level (for hypernatriuria)
	  ○ Cystine
	  ○ pH/urine analysis
	  ○ Volume (24h)
	• Combination tests:
	  ○ Stone analysis + any blood test
	  ○ Stone analysis + any urine test
	  ○ Stone analysis + any blood test + urine test
	  ○ Any blood test + any urine test

	Treatment:
	• Dietary advice:
	  ○ Increase water intake
	• Pharmacological treatment:
	  ○ Thiazides
	  ○ Citrates or bicarbonates
	• No treatment
	• Treatment for specific metabolic abnormality found
	• Combination of treatments

Comparison	Comparator index test: • No test Comparator intervention: • Diet/fluid
Outcomes	• Stone recurrence • Stone interventions (surgery/admission /MET) • Metabolic abnormalities found • Quality of life • Adverse events related to test • Adverse events related to treatment • Number of people receiving treatment
Study design	Randomised controlled trials (RCTs)

1.3 Clinical evidence

1.3.1 Included studies

No relevant clinical studies were identified.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

1.3.2 Excluded studies

See the excluded studies list in appendix I.

1.3.3 Summary of clinical studies included in the evidence review

None.

1.4 Economic evidence

1.4.1 Included studies

No relevant health economic studies were identified.

1.4.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.4.3 Unit costs

Table 2: UK costs of tests

Test	Cost	Sources
Stone analysis	£25.44	1 GC member
Blood tests:		
calcium levels	£1.38 - £.3.33 (a)	3 GC members
uric acid levels	£0.90 - £1.36	3 GC members
Urine tests:		
calcium levels	£2.34 - £2.37	2 GC members
oxalate levels	£20.50 - £30.40	3 GC members
uric acid levels	£1.23 - £2.44	2 GC members
citrate level	£10.51 - £30.40	3 GC members
sodium level	£1.30 - £2.36	3 GC members
Cystine	for spot analysis (screening) = £8.53 more complex testing: = £38.40 - £69.61	3 GC members
Urine pH	£3.09 - £11.28	1 GC member
Volume (24h)	Dependent on tests undertaken on the urine (so including any of the above costs), and some consumable costs for the equipment loaned to the patient.	

(a) £3.33 is for a bone profile

1.5 Resource costs

The committee has made recommendations, for adults, based on this review (see section □) that stone analysis and serum calcium should be 'considered'.

Unlike for stronger recommendations stating that interventions should be adopted, it is not possible to make a judgement about the potential resource impact to the NHS of recommendations regarding interventions that could be used, as uptake is too difficult to predict.

However, the committee noted that where this recommendation is implemented there is not expected to be a substantial impact on resources.

The recommendations made by the committee, for children, based on this review (see section 1.7) are not expected to have a substantial impact on resources.

1.6 Evidence statements

1.6.1 Clinical evidence statements

- No relevant published evidence was identified.

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 Recommendations

A1. Consider stone analysis for adults with ureteric or renal stones.

A2. Consider checking serum calcium for adults with ureteric or renal stones.

A3. Consider referring children and young people with ureteric or renal stones to a paediatric nephrologist or paediatric urologist with expertise in this area for assessment and metabolic investigations.

1.7.1 Research recommendations

What is the clinical and cost effectiveness of full metabolic assessment compared with standard advice alone, in people with recurrent calcium oxalate stones?

1.8 Rationale and impact

1.8.1 Why the committee made the recommendations

Stone analysis and blood testing (serum calcium) allows the diagnosis of rare but treatable conditions such as cystinuria, uric acid stones, and primary hyperparathyroidism. Urine testing allows for the identification of metabolic abnormalities which can be treated and so reduce the risk of future stones.

Evidence showed that there is effective treatment for hypercalciuria and hypocitraturia, and the committee noted that these conditions would be diagnosed with a 24-hour urine test. This shows that understanding underlying metabolic diseases can lead to prevention of stone recurrence. However, no clinical or cost effectiveness evidence for 24-hour urine testing was identified, so they agreed that they could not make a practice recommendation. They agreed to make a research recommendation on the clinical and cost effectiveness of a full metabolic investigation to inform future guidance.

No evidence was also found on stone analysis or blood tests in people who have or have had renal or ureteric stones. The committee agreed that there is variation in current practice, with a full range of metabolic tests being done in some areas and fewer tests in others. They agreed that it is not clear which tests are most useful and whether tests should be offered to all people with a stone or just those at high risk of stone recurrence. The committee agreed that stone analysis and serum calcium tests should be considered for adults.

The committee agreed that current practice for children and young people is highly variable and that referral to a paediatric nephrologist or urologist with expertise for assessment and metabolic investigations should be considered.

1.8.2 Impact of the recommendations on practice

Current practice is varied and metabolic investigation is often based on the interests or preference of individual healthcare professionals, therefore the recommendations may mean a change in practice for some providers. However, the committee agreed that existing centres should have the resources to cope with an increased demand for stone analysis, which is relatively easy to do and is not urgent.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The committee agreed that stone recurrence, stone interventions, metabolic abnormalities found, quality of life, adverse events relating to the test or to the treatment and the number of people receiving treatment were the outcomes that were critical for decision making.

There was no evidence found for any of these outcomes.

1.9.1.2 The quality of the evidence

No evidence was found.

1.9.1.3 Benefits and harms

The committee considered that current practice for metabolic testing is variable and inconsistent, and can include a variety of different tests and combinations of tests. Basic metabolic testing would involve a stone analysis and serum calcium testing, and more advanced testing may include blood tests and urine tests carried out as a 24 hour urine collection, or commonly spot urine ratios in paediatric practice. In current practice, not all laboratories can do all metabolic tests, and therefore the samples may be sent externally to laboratories that can.

The committee discussed the benefits of conducting metabolic tests. They noted that stone analysis allows the composition of the stone to be identified, which can impact on the therapeutic pathway. For instance, there are known treatments for uric acid stones, cystine stones, and APRT deficiency; although the treatment pathway for calcium stones, the most common type of stone, is less well defined. Serum calcium is also usually part of a basic metabolic workup, as this can lead to identification of treatable hypercalcaemic conditions such as primary hyperparathyroidism. The committee agreed that stone analysis and serum calcium should be a minimum standard of testing that can lead to identification of rare but impactful conditions that could be managed and treated. Given the lack of evidence however, and also lack of certainty on the cost effectiveness of these tests, consider recommendations were made.

The committee also discussed that urine testing (different abnormalities can be tested for from a urine sample) can lead to the identification of conditions such as hypercalciuria and hypocitraturia, and noted that these conditions have been identified in the Prevention of Recurrence review (chapter K) as having effective treatments to prevent a future stone. However, the committee were unclear on both the clinical and cost effectiveness of these tests, and therefore agreed that a research recommendation would be beneficial in this area, to assess whether a full laboratory metabolic work up has additional benefit clinically, compared to stone analysis alone, and to assess the cost effectiveness of this. The committee agreed that this guidance could potentially reduce the amount of unnecessary testing, and increase the uptake of more specific, targeted tests. This may also lead to standardisation of metabolic testing within the UK.

The committee considered current practice regarding metabolic and laboratory testing in children and young people and noted that there is much variability around the country. They agreed that referral to a paediatric nephrologist or paediatric urologist with expertise in this area for assessment and metabolic investigations should be considered, but noted that many centres have paediatricians with an interest in nephrology who share care with a paediatric nephrologist who could undertake such investigations themselves.

1.9.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

Unit costs were presented to the committee of different tests that might be undertaken as part of metabolic investigation. These were based on costs from the committee member's hospitals. A stone analysis costs around £25. Blood tests are low cost at a few pounds. Urine tests are much more variable depending on the test themselves, with testing for citrate, oxalate, or cystine being the most expensive.

Ideally the committee wanted to know who should have metabolic testing (for example, perhaps only individuals considered high risk like recurrent stone formers), and what tests should be used. A stone analysis for example that provides information on the composition of the stone would direct the usefulness of investigation of any further abnormalities noted in blood and/or urine tests. The comparators involved are different combinations of tests, and can vary in cost depending on what tests are involved.

The trade-offs involved around metabolic testing are dependent on the prevalence of the conditions that will be identified, what management might be involved - and the effectiveness of the management at changing the probability of recurrence. Uncertainty around these factors for all the conditions that metabolic tests might predict makes it difficult to infer cost effectiveness. There are however two groups in particular where the prevalence is small but identifying the metabolic abnormality would lead to management pathways that are specific and well established – these are uric acid and cystine stones, and therefore there is a large benefit to identifying these people. The largest group, which is also more difficult to manage is the mixed calcium stones.

The committee consensus was that there should be a minimum standard on the type of metabolic work-up that should take place. Different tests provide different information. A stone analysis can identify the stone composition, then this can help identify the rare conditions that have management pathways (uric acid stones and cystine stones). Serum calcium can also identify primary hyperparathyroidism as those with high serum calcium would then have a parathyroid hormone test which would diagnose this. There was no clinical or economic evidence to support this, as the cost effectiveness, as mentioned above would depend on the prevalence of these rare conditions - and the benefit identification would lead to - traded-off against the cost of testing an initial population with stones. Therefore a consider recommendation was made based on committee consensus.

Anecdotally, more than half of patients do not have a stone available for analysis. Also not all hospitals have the facilities to undertake a stone analysis and the stone would have to be sent to another laboratory for analysis. As this was a consider recommendation, the resource impact of this is unclear. A stone is also more likely to be available if a patient had a URS, rather than an SWL (as the stone was fragmented and passed on its own – unless the patient brought it in), so the population this would apply to, is not likely to be the whole renal stones population. The committee also agreed that more stones being analysed is not likely to have a service impact as the stones can be analysed with the current services available.

A workup involving more tests in the majority of stone formers that do not fit into these rare disease groups (calcium stone formers) would be more costly, and this is the subject of a research recommendation to assess whether a full laboratory metabolic work up has additional benefit, compared to stone analysis alone, and to assess the cost effectiveness of this.

In children, it is established practice that they would have a more thorough metabolic workup than adults due to higher lifetime risk of recurrence and greater likelihood of an underlying genetic/metabolic cause than adults. Practice varies as to what tests specifically this might

include. The committee opinion was that ideally children should be referred to a paediatric nephrologist or paediatric urologist who has expertise in laboratory tests for metabolic conditions, for appropriate investigation. The child population with renal stones is very small.

1.9.3 Other factors the committee took into account

In the review on the prevention of recurrence, the committee made recommendations for certain interventions in subgroups of people with particular types of stones. This means that a stone analysis to be able to identify the type of stone would be a precursor to offering these interventions. As it has not been proven whether a stone analysis is cost effective in all patients, then those recommendations are 'consider' recommendations to reflect the strength of certainty in the balance of benefits and costs. This is because as explained above, assessing cost effectiveness of testing also requires knowledge of the effectiveness of interventions. Clinical questions often assess individual parts of a pathway, but these need to be taken together when assessing cost effectiveness because individual parts of a pathway have an impact on the rest of the pathway.

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Appendices

Appendix A: Review protocols

Question number: 5.1

Relevant section of Scope: 5 Metabolic investigations

Field	Content
Review question	In people with renal or ureteric stones, what is the clinical and cost effectiveness of stone analysis, blood test and urine test compared to no test, when each is followed by the appropriate treatment for renal and ureteric stones, in order to improve patient outcomes?
Type of review question	Diagnostic test-and-treat A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To evaluate the clinical effectiveness of different metabolic tests/workups involving various tests when followed up by treatment for people with renal and ureteric stones
Eligibility criteria – population / disease / condition / issue / domain	All people with renal or ureteric stones.

Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	**Index tests:**
	• Stone analysis
	• Blood tests:
	  ○ calcium levels (for hypercalcaemia)
	  ○ uric acid levels (for hyper- or hypo- uricaemia)
	• Urine tests:
	  ○ calcium levels (for hypercalciuria)
	  ○ oxalate levels (for hyperoxaluria)
	  ○ uric acid levels (for hyper- or hypo- uricosuria)
	  ○ citrate level (for hypocitraturia)
	  ○ sodium level (for hypernatriuria)
	  ○ Cystine
	  ○ pH/urine analysis
	  ○ Volume (24h)
	• Combination tests:
	  ○ Stone analysis + any blood test
	  ○ Stone analysis + any urine test
	  ○ Stone analysis + any blood test + urine test
	  ○ Any blood test + any urine test
	
	Treatment:
	• Dietary advice:
	  ○ Increase water intake
	• Pharmacological treatment:
	  ○ Thiazides
	  ○ Citrates or bicarbonates
	• No treatment
	• Treatment for specific metabolic abnormality found
	Combination of treatments

Eligibility criteria – comparator(s) / control or reference (gold) standard	Comparator index test: No test Comparator intervention: Diet/fluid
Outcomes and prioritisation	Stone recurrence Stone interventions (surgery/admission /MET) Metabolic abnormalities found Quality of life Adverse events related to test Adverse events related to treatment Number of people receiving treatment
Eligibility criteria – study design	Randomised trials
Other inclusion exclusion criteria	-
Proposed sensitivity / subgroup analysis, or meta-regression	Stratification – groups that cannot be combined: Adults (≥16 years) Children and young people (<16 years) First stone formers Recurrent stone formers Obese people People with malabsorptive gut disease Subgroups: People with diabetes
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	Endnote for bibliography, citations, sifting and reference management. EviBASE will be used for data extraction and quality assessment for clinical studies. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library Date: all years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – all years Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10033
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.

Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ [Please document any deviations/alternative approach when GRADE isn't used or if a modified GRADE approach has been used for non-intervention or non-comparative studies.]
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Andrew Dickinson in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1 **Table 3: Health economic review protocol**

Review question	**All questions – health economic evidence**
Objectives	To identify economic studies relevant to any of the review questions.

Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G *[in the Full guideline]*.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the 2014 NICE guidelines manual.[13] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the Committee if required. The ultimate aim is to include economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the Committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* • Cost-utility analysis (most applicable).

	• Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will have been excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the clinical effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review. [Add cross reference]

B.1 Clinical search literature search strategy

A search was constructed using the following approach:

- Population AND Prognostic/risk factor terms AND Study filter(s)

A separate search was performed to identify studies about metabolic investigations (test-and-treat approach).

B.1.1 Metabolic investigations

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 7 December 2017	Exclusions Observational studies Diagnostic tests studies Prognostic studies
Embase (OVID)	1974 – 7 December 2017	Exclusions Observational studies Diagnostic tests studies Prognostic studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 12 of 12 CENTRAL to 2017 Issue 11 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

1 **Medline (Ovid) search terms**

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Hypercalcemia/
28.	(hypercalcemia or hypercalcaemia).ti,ab.
29.	Hypercalciuria/
30.	hypercalciuria.ti,ab.
31.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (calcium or Ca)).ti,ab.
32.	exp Hyperoxaluria/
33.	hyperoxaluria.ti,ab.
34.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (oxalate* or C2O4-2 or ethanedioate)).ti,ab.
35.	hyperuricosuria.ti,ab.
36.	Hyperuricemia/
37.	(hyperuricemia or hyperuricaemia).ti,ab.
38.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 uric acid).ti,ab.
39.	hypernatriuria.ti,ab.
40.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (sodium or Na)).ti,ab.

41.	Cystine/
42.	Cystinuria/
43.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 cystine).ti,ab.
44.	hypocitraturia.ti,ab.
45.	((reduce* or decrease* or low* or less* or drop*) adj3 citrate*).ti,ab.
46.	hypomagnesuria.ti,ab.
47.	((reduce* or decrease* or low* or less* or drop*) adj3 (magnesium or Mg)).ti,ab.
48.	((metabolic* or blood* or urine) adj2 (analys* or test* or investigat*)).ti,ab.
49.	(urinalysis or full blood count or FBC).ti,ab.
50.	or/27-49
51.	26 and 50
52.	prognosis/
53.	(predict* or prognos*).ti,ab.
54.	Logistic models/
55.	Disease progression/
56.	or/52-55
57.	Epidemiologic studies/
58.	Observational study/
59.	exp Cohort studies/
60.	(cohort adj (study or studies or analys* or data)).ti,ab.
61.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
62.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
63.	Controlled Before-After Studies/
64.	Historically Controlled Study/
65.	Interrupted Time Series Analysis/
66.	(before adj2 after adj2 (study or studies or data)).ti,ab.
67.	or/57-66
68.	exp case control study/
69.	case control*.ti,ab.
70.	or/68-69
71.	67 or 70
72.	Cross-sectional studies/
73.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
74.	or/72-73
75.	67 or 74
76.	67 or 70 or 74
77.	exp "sensitivity and specificity"/
78.	(sensitivity or specificity).ti,ab.
79.	((pre test or pretest or post test) adj probability).ti,ab.
80.	(predictive value* or PPV or NPV).ti,ab.
81.	likelihood ratio*.ti,ab.
82.	likelihood function/
83.	((area under adj4 curve) or AUC).ti,ab.

84.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
85.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
86.	gold standard.ab.
87.	or/77-86
88.	56 or 76 or 87
89.	51 and 88

1 **Embase (Ovid) search terms**

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	*hypercalcemia/
26.	(hypercalcemia or hypercalcaemia).ti,ab.
27.	*hypercalciuria/
28.	hypercalciuria.ti,ab.
29.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (calcium or Ca)).ti,ab.
30.	exp *hyperoxaluria/
31.	hyperoxaluria.ti,ab.
32.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (oxalate* or C2O4-2 or ethanedioate)).ti,ab.
33.	hyperuricosuria.ti,ab.
34.	*hyperuricemia/

35.	(hyperuricemia or hyperuricaemia).ti,ab.
36.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 uric acid).ti,ab.
37.	hypernatriuria.ti,ab.
38.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (sodium or Na)).ti,ab.
39.	*cystine/
40.	*cystinuria/
41.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 cystine).ti,ab.
42.	hypocitraturia.ti,ab.
43.	((reduce* or decrease* or low* or less* or drop*) adj3 citrate*).ti,ab.
44.	hypomagnesuria.ti,ab.
45.	((reduce* or decrease* or low* or less* or drop*) adj3 (magnesium or Mg)).ti,ab.
46.	((metabolic* or blood* or urine) adj2 (analys* or test* or investigat*)).ti,ab.
47.	(urinalysis or full blood count or FBC).ti,ab.
48.	or/25-47
49.	24 and 48
50.	Clinical study/
51.	Observational study/
52.	family study/
53.	longitudinal study/
54.	retrospective study/
55.	prospective study/
56.	cohort analysis/
57.	follow-up/
58.	cohort*.ti,ab.
59.	57 and 58
60.	(cohort adj (study or studies or analys* or data)).ti,ab.
61.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
62.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
63.	(before adj2 after adj2 (study or studies or data)).ti,ab.
64.	or/50-56,59-63
65.	exp case control study/
66.	case control*.ti,ab.
67.	or/65-66
68.	64 or 67
69.	cross-sectional study/
70.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
71.	or/69-70
72.	64 or 71
73.	64 or 67 or 71
74.	exp "sensitivity and specificity"/
75.	(sensitivity or specificity).ti,ab.
76.	((pre test or pretest or post test) adj probability).ti,ab.

77.	(predictive value* or PPV or NPV).ti,ab.
78.	likelihood ratio*.ti,ab.
79.	((area under adj4 curve) or AUC).ti,ab.
80.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
81.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
82.	diagnostic accuracy/
83.	diagnostic test accuracy study/
84.	gold standard.ab.
85.	or/74-84
86.	exp prognosis/
87.	prognostic assessment/
88.	(predict* or prognos*).ti,ab.
89.	disease course/
90.	statistical model/
91.	or/86-90
92.	73 or 85 or 91
93.	49 and 92

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Urolithiasis] explode all trees
#2.	(nephrolitiasis or nephrolith or urolithiasis):ti,ab
#3.	((renal or kidney or urinary or ureteric or ureteral or ureter) near/2 (stone* or calculi or calculus or calculosis or lithiasis or colic)):ti,ab
#4.	(stone disease*):ti,ab
#5.	((calculi or calculus or calcium oxalate or cystine) near/2 (crystal* or stone* or lithiasis)):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Hypercalcemia] explode all trees
#8.	(hypercalcemia or hypercalcaemia):ti,ab
#9.	MeSH descriptor: [Hypercalciuria] explode all trees
#10.	hypercalciuria:ti,ab
#11.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) near/3 (calcium or Ca)):ti,ab
#12.	MeSH descriptor: [Hyperoxaluria] explode all trees
#13.	hyperoxaluria:ti,ab
#14.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) near/3 (oxalate* or C2O4-2 or ethanedioate)):ti,ab
#15.	hyperuricosuria:ti,ab
#16.	MeSH descriptor: [Hyperuricemia] explode all trees
#17.	(hyperuricemia or hyperuricaemia):ti,ab
#18.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) near/3 uric acid):ti,ab
#19.	hypernatriuria:ti,ab
#20.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) near/3 (sodium or Na)):ti,ab
#21.	MeSH descriptor: [Cystine] explode all trees
#22.	MeSH descriptor: [Cystinuria] explode all trees

#23.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) near/3 cystine):ti,ab
#24.	hypocitraturia:ti,ab
#25.	((reduce* or decrease* or low* or less* or drop*) near/3 citrate*):ti,ab
#26.	hypomagnesuria:ti,ab
#27.	((reduce* or decrease* or low* or less* or drop*) near/3 (magnesium or Mg)):ti,ab
#28.	((metabolic* or blood* or urine) near/2 (analys* or test* or investigat*)):ti,ab
#29.	(urinalysis or full blood count or FBC):ti,ab
#30.	(or #7-#29)
#31.	#6 and #30

B.1.2 Metabolic investigations – test-and-treat approach

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 23 January 2018	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 23 January 2018	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 1 of 12 CENTRAL to 2018 Issue 12 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16

18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	((stone* or calculi or calculus or crystal*) adj3 (analys* or test* or investigat* or evaluat* or etiolog* or morpholog* or compos*)).ti,ab.
28.	Chemistry Techniques, Analytical/
29.	(chemical adj (analys* or analytic* or test* or investigat* or technique*)).ti,ab.
30.	Crystallography/
31.	(optical crystallography or stereomicroscopy or thermogravimetry or thermal analysis).ti,ab.
32.	((scanning electron or polari?ed or polari?ing) adj microscopy).ti,ab.
33.	X-Ray Diffraction/
34.	(x ray adj2 diffraction).ti,ab.
35.	Spectrum Analysis/
36.	(spectrum adj2 analy*).ti,ab.
37.	X-Ray Absorption Spectroscopy/
38.	((x ray or xray or infra red or infrared or Raman or Fourier) adj3 spectroscopy).ti,ab.
39.	(dual adj (source or energy) adj (CT or computed tomograph*)).ti,ab.
40.	or/27-39
41.	((metabolic* or blood* or urine or 24h or 24 hour) adj2 (analys* or test* or investigat*)).ti,ab.
42.	(urinalysis or full blood count or FBC).ti,ab.
43.	Hypercalcemia/
44.	(hypercalcemia or hypercalcaemia).ti,ab.
45.	Hypercalciuria/
46.	hypercalciuria.ti,ab.
47.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (calcium or Ca)).ti,ab.
48.	Hyperuricemia/
49.	(hyperuricemia or hyperuricaemia or hyperuricosuria or hyper uricosuria or hypo uricosuria or hypouricosuria).ti,ab.
50.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten* or reduce* or decrease* or low* or less* or drop*) adj3 uric acid).ti,ab.
51.	exp Hyperoxaluria/
52.	hyperoxaluria.ti,ab.
53.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (oxalate* or C2O4-2 or ethanedioate)).ti,ab.
54.	hypocitraturia.ti,ab.
55.	((reduce* or decrease* or low* or less* or drop*) adj3 citrate*).ti,ab.
56.	hypernatriuria.ti,ab.

57.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (sodium or Na)).ti,ab.
58.	Cystine/
59.	Cystinuria/
60.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 cystine).ti,ab.
61.	or/40-60
62.	26 and 61
63.	randomized controlled trial.pt.
64.	controlled clinical trial.pt.
65.	randomi#ed.ti,ab.
66.	placebo.ab.
67.	randomly.ti,ab.
68.	Clinical Trials as topic.sh.
69.	trial.ti.
70.	or/63-69
71.	Meta-Analysis/
72.	exp Meta-Analysis as Topic/
73.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
74.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
75.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
76.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
77.	(search* adj4 literature).ab.
78.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
79.	cochrane.jw.
80.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
81.	or/71-80
82.	62 and (70 or 81)

1 **Embase (Ovid) search terms**

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.

14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	stone analysis/
26.	((stone* or calculi or calculus or crystal*) adj3 (analys* or test* or investigat* or evaluat* or etiolog* or morpholog* or compos*)).ti,ab.
27.	*chemical analysis/
28.	(chemical adj (analys* or analytic* or test* or investigat* or technique*)).ti,ab.
29.	*crystallography/
30.	(optical crystallography or stereomicroscopy or thermogravimetry or thermal analysis).ti,ab.
31.	((scanning electron or polari?ed or polari?ing) adj microscopy).ti,ab.
32.	*x ray diffraction/
33.	(x ray adj2 diffraction).ti,ab.
34.	*spectroscopy/
35.	*x ray absorption spectroscopy/
36.	((x ray or xray or infra red or infrared or Raman or Fourier) adj3 spectroscopy).ti,ab.
37.	(dual adj (source or energy) adj (CT or computed tomograph*)).ti,ab.
38.	or/25-37
39.	*urinalysis/
40.	((metabolic* or blood* or urine or 24h or 24 hour) adj2 (analys* or test* or investigat*)).ti,ab.
41.	(urinalysis or full blood count or FBC).ti,ab.
42.	*hypercalcemia/
43.	(hypercalcemia or hypercalcaemia).ti,ab.
44.	*hypercalciuria/
45.	hypercalciuria.ti,ab.
46.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (calcium or Ca)).ti,ab.
47.	*hyperuricemia/
48.	(hyperuricemia or hyperuricaemia or hyperuricosuria or hyper uricosuria or hypo uricosuria or hypouricosuria).ti,ab.
49.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten* or reduce* or decrease* or low* or less* or drop*) adj3 uric acid).ti,ab.
50.	exp *hyperoxaluria/
51.	hyperoxaluria.ti,ab.
52.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (oxalate* or C2O4-2 or ethanedioate)).ti,ab.
53.	hypocitraturia.ti,ab.

54.	((reduce* or decrease* or low* or less* or drop*) adj3 citrate*).ti,ab.
55.	hypernatriuria.ti,ab.
56.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 (sodium or Na)).ti,ab.
57.	*cystine/
58.	*cystinuria/
59.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) adj3 cystine).ti,ab.
60.	or/38-59
61.	24 and 60
62.	random*.ti,ab.
63.	factorial*.ti,ab.
64.	(crossover* or cross over*).ti,ab.
65.	((doubl* or singl*) adj blind*).ti,ab.
66.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
67.	crossover procedure/
68.	single blind procedure/
69.	randomized controlled trial/
70.	double blind procedure/
71.	or/62-70
72.	systematic review/
73.	meta-analysis/
74.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
75.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
76.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
77.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
78.	(search* adj4 literature).ab.
79.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
80.	cochrane.jw.
81.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
82.	or/72-81
83.	61 and (71 or 82)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Urolithiasis] explode all trees
#2.	(nephrolitiasis or nephrolith or urolithiasis):ti,ab
#3.	((renal or kidney or urinary or ureteric or ureteral or ureter) near/2 (stone* or calculi or calculus or calculosis or lithiasis or colic)):ti,ab
#4.	(stone disease*):ti,ab
#5.	((calculi or calculus or calcium oxalate or cystine) near/2 (crystal* or stone* or lithiasis)):ti,ab
#6.	(or #1-#5)
#7.	((stone* or calculi or calculus or crystal*) near/3 (analys* or test* or investigat* or evaluat* or etiolog* or morpholog* or compos*)):ti,ab
#8.	MeSH descriptor: [Chemistry Techniques, Analytical] explode all trees

#9.	chemical near/1 (analys* or analytic* or test* or investigat* or technique*):ti,ab
#10.	MeSH descriptor: [Crystallography] explode all trees
#11.	(optical crystallography or stereomicroscopy or thermogravimetry or thermal analysis):ti,ab
#12.	((scanning electron or polari?ed or polari?ing) near microscopy):ti,ab
#13.	MeSH descriptor: [X-Ray Diffraction] explode all trees
#14.	(x ray near/2 diffraction):ti,ab
#15.	MeSH descriptor: [Spectrum Analysis] explode all trees
#16.	(spectrum near/2 analy*):ti,ab
#17.	MeSH descriptor: [X-Ray Absorption Spectroscopy] explode all trees
#18.	((x ray or xray or infra red or infrared or Raman or Fourier) near/3 spectroscopy):ti,ab
#19.	(dual near/1 (source or energy) near/1 (CT or computed tomograph*)):ti,ab
#20.	(or #7-#19)
#21.	((metabolic* or blood* or urine or 24h or 24 hour) near/2 (analys* or test* or investigat*)):ti,ab
#22.	(urinalysis or full blood count or FBC):ti,ab
#23.	MeSH descriptor: [Hypercalcemia] explode all trees
#24.	(hypercalcemia or hypercalcaemia):ti,ab
#25.	MeSH descriptor: [Hypercalciuria] explode all trees
#26.	hypercalciuria:ti,ab
#27.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) near/3 (calcium or Ca)):ti,ab
#28.	MeSH descriptor: [Hyperuricemia] explode all trees
#29.	(hyperuricemia or hyperuricaemia or hyperuricosuria or hyper uricosuria or hypo uricosuria or hypouricosuria):ti,ab
#30.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten* or reduce* or decrease* or low* or less* or drop*) near/3 uric acid):ti,ab
#31.	MeSH descriptor: [Hyperoxaluria] explode all trees
#32.	hyperoxaluria:ti,ab
#33.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) near/3 (oxalate* or C2O4-2 or ethanedioate)):ti,ab
#34.	hypocitraturia:ti,ab
#35.	((reduce* or decrease* or low* or less* or drop*) near/3 citrate*):ti,ab
#36.	hypernatriuria:ti,ab
#37.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) near/3 (sodium or Na)):ti,ab
#38.	MeSH descriptor: [Cystine] explode all trees
#39.	MeSH descriptor: [Cystinuria] explode all trees
#40.	((high* or raise* or increase* or elevat* or excess* or lift* or uplift* or inflat* or heighten*) near/3 cystine):ti,ab
#41.	(or #20-#40)
#42.	#6 and #41

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to renal and ureteric stones population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for

Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies.

Table 6: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 9 March 2018	Exclusions Health economics studies
Embase	2014 – 9 March 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 9 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/

31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

1 **Embase (Ovid) search terms**

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/

26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

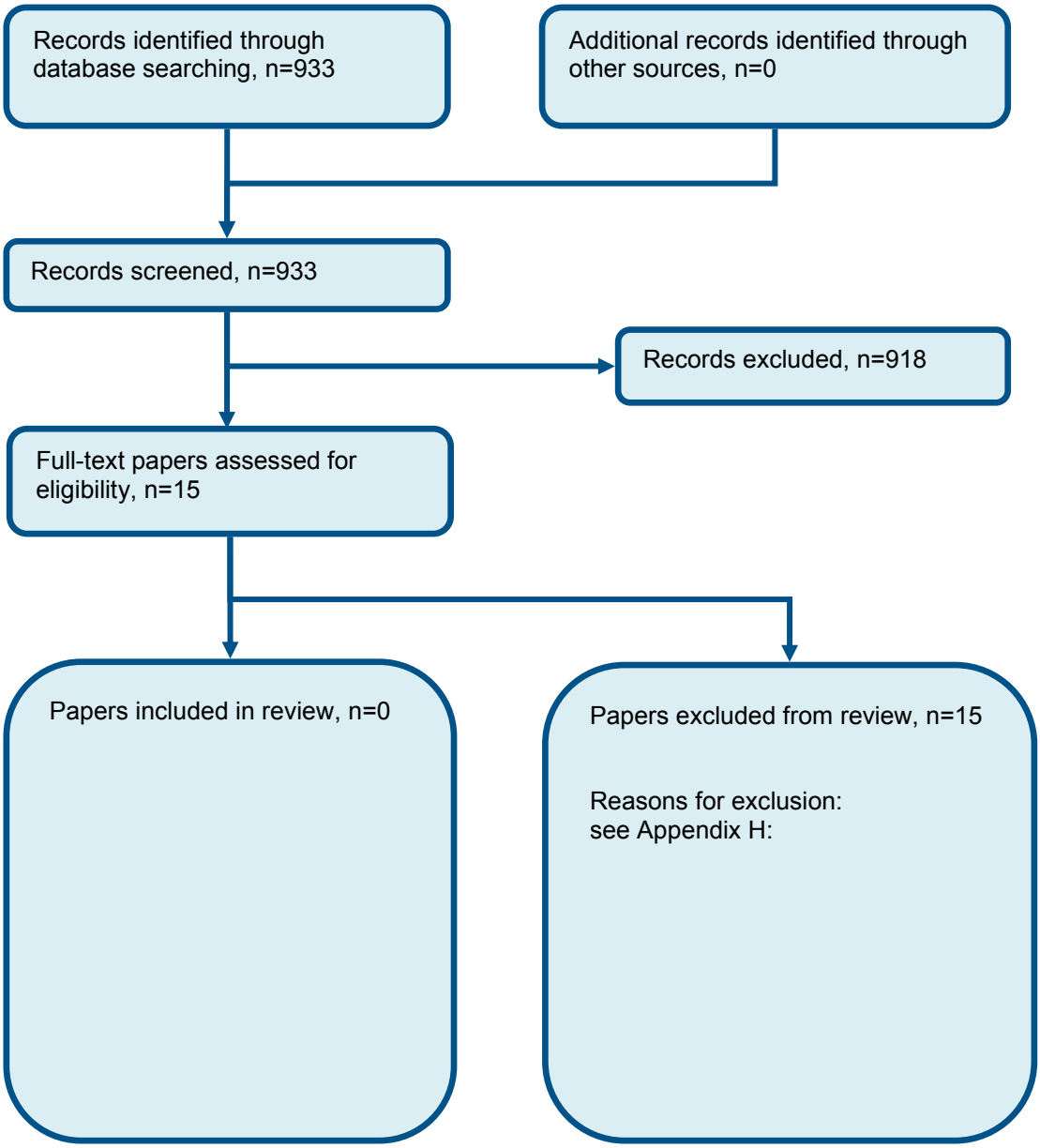
1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR urolithiasis EXPLODE ALL TREES
#2.	(((nephrolitiasis or nephrolith or urolithiasis)))
#3.	((((renal or kidney or urinary or ureteric or ureteral or ureter or urethra*) adj2 (stone* or calculi or calculus or calculosis or lithiasis or colic))))
#4.	((stone disease*))
#5.	((((calculi or calculus) adj2 (stone* or lithiasis))))
#6.	(#1 OR #2 OR #3 OR #4 OR #5)

2
3

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of metabolic investigations



Appendix D: Clinical evidence tables

None.

Appendix E: Forest plots

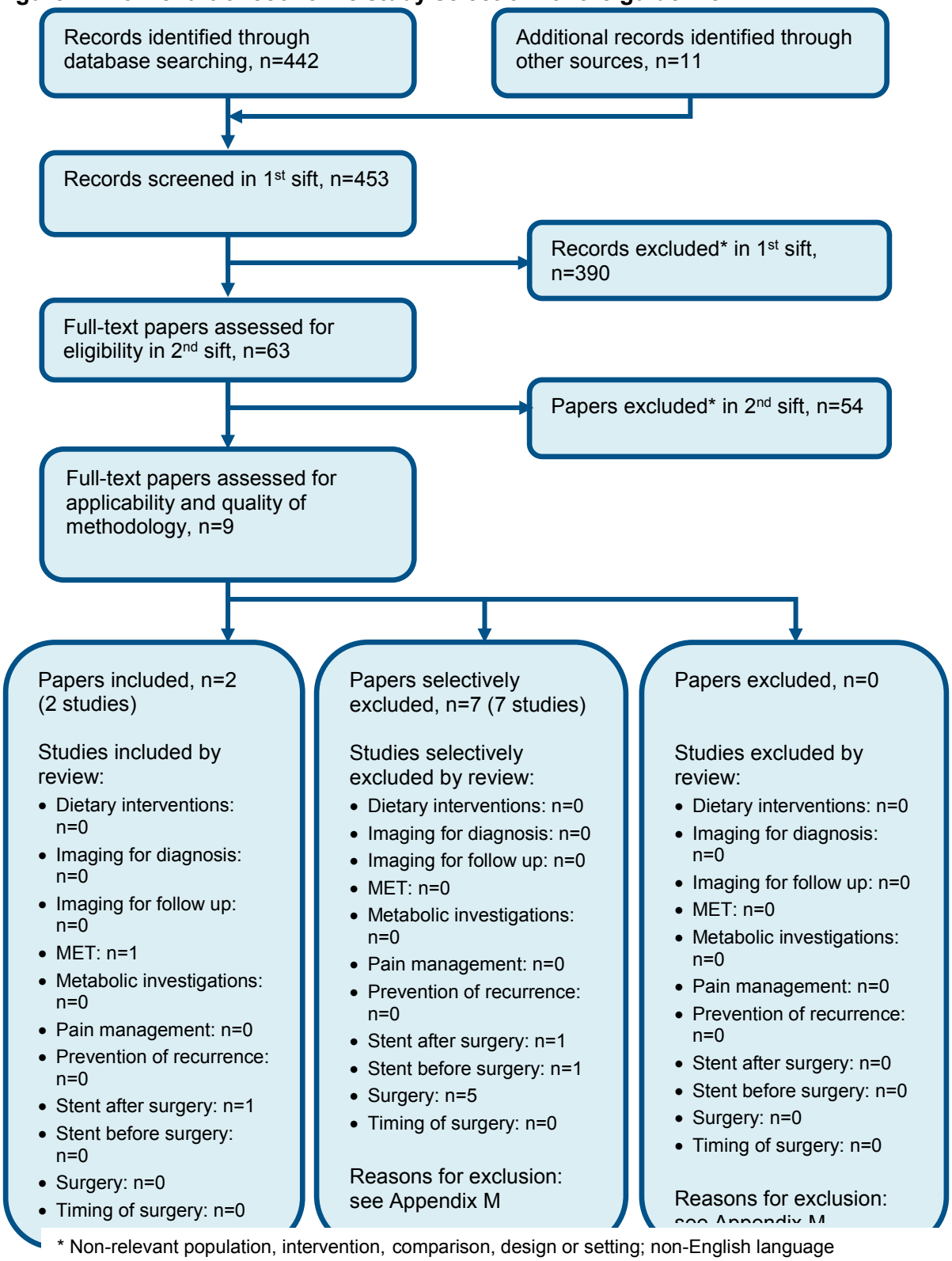
None

Appendix F: GRADE tables

None.

Appendix G: Health economic evidence selection

Figure 2: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 7: Studies excluded from the clinical review

Study	Exclusion reason
Auge 2006[1]	Incorrect study design (case-control study)
Channa 2007[2]	Incorrect study design (cohort study)
Clifford-Mobley 2016[3]	Incorrect population (people with hyperoxaluria)
Da Silva 2010[4]	Incorrect study design (cross-sectional study)
Dhandapani 2016[5]	Incorrect study design (cohort study)
Durgawale 2010[6]	Incorrect study design (cohort study)
Ferraro 2017[7]	Incorrect study design (regression analysis of recurrence rate)
Gambaro 2016[8]	Incorrect study design (narrative review and consensus statements)
Hess 2012[9]	Incorrect study design (non-systematic review)
Krautschick 1999[10]	Incorrect study design (non-systematic review)
Naseri 2010[12]	Incorrect study design (cohort study)
Naseri 2013[11]	Incorrect study design (non-systematic review)
Orakzai 2004[14]	Incorrect study design (cohort study)
Skolarikos 2015[15]	Incorrect study design (narrative review and consensus statements)
Tiselius 2017[16]	Incorrect study design (non-systematic review)

I.2 Excluded health economic studies

None

Appendix J: Research recommendations

J.1 Full metabolic assessment

Research Question: What is the clinical and cost effectiveness of full metabolic assessment compared with standard advice alone, in people with recurrent calcium oxalate stones?

Background

Prevalence of stone risk factors in a single centre study of a London medical stone clinic: low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia was 5.6%, 38%, 7.9%, 18% and 23% respectively (Ferraro 2015 QJM)

There is no accepted practice in terms of which, if any, of the identified biochemical risk factors are treated.

Protocol treatments for each test result are given below. Efficacy is proven only for low urine volume. Stone analysis by infra-red spectroscopy – allows precise diagnosis of non-calcium stones.

- low urine volume <2L/24hr - increase fluid intake >2.5 L/24h aiming to pass >2L urine/24h.
- hypercalciuria >7 mmol/24hr (6.5 mmol/24h in females): salt reduction, > 10 mmol/24h: salt reduction and thiazide diuretic
- hyperoxaluria >400 micromole/24hr: avoid high oxalate foods, take/recommend calcium supplements
- hyperuricosuria > 4.0 mmol/24hr - reduce animal protein intake, potassium citrate to enable urine pH>6.5, allopurinol if gout
- hypocitraturia <2.5 mmol/24hr - potassium citrate 10 ml (28 mmol) tds

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PICO question	**Population:** Adults with multiple or recurrent renal or ureteric stones (two or more confirmed stone episodes within the last 5 years) made predominantly of calcium oxalate, where there is no clinically obvious underlying cause. All have received general diet and fluid advice and basic safety blood tests.
	Intervention:
	• Test/treatment
	  ○ no further testing or treatment (diet and fluid advice only)
	  ○ full metabolic assessment (panel of blood and urine tests - see below) and specific treatment of each identified risk factor
	Comparator: each other
	Outcomes:
	Primary: stone related events (including spontaneous stone passage, flank pain, infections, new stone growth or the need for intervention)
	Secondary: metabolic abnormalities found, Quality of life (EQ-5D-3L), cost- per QALY, , resource use: metabolic abnormalities corrected; metabolic interventions provided (tests done, treating abnormalities), compliance.
	Follow up: 36-60 months

Importance to patients or the population	Recurrent kidney stone formers often have severe disruption to their lives with frequent episodes of severe pain and multiple surgical procedures. A number of RCTs have shown the benefit of treating certain metabolic abnormalities associated with kidney stones (e.g. hypercalciuria, hypocitraturia). There are no test-treat RCTs assessing the effectiveness of full metabolic assessment to detect abnormalities which might be corrected to help reduce stone related events. The research will allow an evidenced approach to the metabolic evaluation of idiopathic calcium oxalate stone forming patients, which is the largest single group of patients with renal and ureteric stones. Currently, metabolic evaluation consists of non-standardised sequence of tests, is not applied systematically to this patient group, and the outcomes are often biochemical rather than symptom-based.
Relevance to NICE guidance	This research will reduce the existing uncertainty regarding which metabolic tests should be done in the largest single group of patients with renal and ureteric stones. It will assess the clinical effectiveness and cost-effectiveness of a full test and treat approach. There is currently no evidence in a UK based study on which to base recommendations. It will enable future guidelines to clearly recommend an evidence based

	approach to the prevention of recurrent stones in this large group of patients.
Relevance to the NHS	Kidney stones are very common and there has been a large increase in hospital episodes and resource use for kidney stones. It is thought that this is a public health problem related to dietary changes and increases in obesity hypertension and diabetes. Kidney stone prevention is very patchy around the country and there is much uncertainty about the value of full metabolic assessment. This research would standardise the approach to the metabolic evaluation so giving the largest single group of stone patients equal access to the correct evaluation and treatment. By correctly assessing patients and treating appropriately the incidence of recurrent stone episodes should be reduced so reducing the need to access health resources, in particular imaging and surgery. Equally, information would be obtained on the cost, necessity and benefit of metabolic tests which would then inform decisions on whether testing should be a tertiary level or more generally available NHS service.
National priorities	There is a strong link between diabetes, obesity and kidney stones and limiting the impact of these conditions is one of the top research priorities of the NHS. It is also a priority to test interventions and maximize effectiveness and cost-effectiveness.
Current evidence base	The current evidence base does not allow the Guideline Committee to make a recommendation apart from a consensus recommendations and therefore the grade and the recommendations are not an improvement on other published guidelines. There is a need for a stronger evidence based recommendation of the correct use of metabolic testing in patients with renal and ureteric stones.
Equality	Currently full metabolic evaluation is available to patients without defined criteria, and in only a handful of centres throughout the country. This research will allow a case to be made for more accessible testing if required, or concentration in a specialist centres on a referral basis.
Study design	Diagnostic test and treat
Feasibility	The time scale will need to be 36-60 months to ensure adequate follow-up so that differences in interventions can be seen between the groups. The cost will be acceptable as the metabolic test panel is standard in the NHS centres that provide it.
Other comments	This trial is important to ensure that metabolic evaluation is standardised in this large stone-forming group, and therefore the correct treatment to reduce their lifetime risk of recurrent stone episodes. Previous large scale studies have all been epidemiological or have used biochemical outcomes, rather than patient outcomes, and have not assessed cost-effectiveness.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

1