National Institute for Health and Care Excellence

Guideline version (Final)

Gout: diagnosis and management

[B] Evidence review for what signs and symptoms indicate gout as a possible diagnosis?

NICE guideline NG219

Evidence reviews underpinning recommendations 1.1.1 to 1.1.6 in the NICE guideline

June 2022

Final

National Institute for Health and Care Excellence

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Contents

1 What signs and symptoms indicate gout as a possible diagnosis?

1.1 Review question: What signs and symptoms indicate gout as a possible diagnosis?

1.1.1 Introduction

Effective management of gout depends in part upon the ability of health professionals to recognise and diagnose gout. It more commonly affects men but can also affect women, particularly post menopause. It is more common in middle-aged and elderly people. Gout is typically diagnosed in primary care following an acute presentation with a history of clinical symptoms and presentation of clinical signs of an acute flare of gout. Despite it being the commonest inflammatory arthritis in the UK it is a condition that is not always recognised by health professionals.

This evidence review evaluates the diagnostic accuracy of the symptoms and signs to identify whether gout is present.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (18 years and older) with suspected gout Strata: people with pre-existing osteo-arthritis Exclusion: People with calcium pyrophosphate crystal deposition (CPPD), also known as pseudogout
Target condition	Gout
Signs and symptoms	• Distribution of affected joints (monoarticular /polyarticular involvement, which joints e.g first metatarsophalangeal joint) • Previous episodes of similar acute arthritis • Rapid onset of severe pain • Rapid onset of swelling • Erythema • Joint tenderness • Tophi • Overnight onset (nocturnal onset) • Combinations of the above
Reference standards	Confirmed diagnosis of gout by various means: • Joint aspiration (urate crystals are observed in synovial fluid or tophi) is the gold standard. • X-ray • Ultrasound • Dual-energy CT (DECT)

	The reference standards would be analysed separately.
Outcomes	• Sensitivity and specificity.
Study design	• Diagnostic accuracy cross-sectional studies. • Systematic reviews of diagnostic accuracy cross-sectional studies.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

A search was conducted for cross-sectional studies which assess the diagnostic accuracy of particular signs and symptoms for identifying whether gout is present. Each sign/symptom was compared to a reference standard test that confirmed the diagnosis of gout.

One diagnostic accuracy study was included in the review: Malik 2009,[35] this is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below in **Table 3**. The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as sensitivity/specificity =0.8 above which a test would be recommended and 0.5 below which a test is of no clinical use.

See also the study selection flow chart in Appendix C, sensitivity and specificity forest plots in Appendix E, and study evidence tables in Appendix D.

1.1.4.2 Excluded studies

There were systematic reviews retrieved from the search which did not match our protocol and were therefore excluded. The references from these systematic reviews were checked for any relevant studies for this review.

See the excluded studies list in Appendix H.

1.1.5 Summary of studies included in the diagnostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Target condition	Signs/symptoms	Reference standard	Comments
Malik 200935	N=82 Participants from the Department of Veterans Affairs rheumatology clinic were selected if they had had synovial fluid aspirated and analysed at some time with compensated light microscopy. USA	Gout	More than 1 attack of acute arthritis; maximum inflammation developed within 1 day; monoarthritis attack, erythema, first MTP joint painful or swollen; unilateral tarsal joint attack; tophus (proven or suspected); painful joint swelling. Abrupt onset, clearing in 1-2 weeks initially, started at night.	Joint aspiration of synovial fluid analysis	There was an error in the values given for maximum inflammation developed within 1 day but this was calculated correctly from the sensitivity and specificity.

See Appendix D for full evidence tables

1.1.6 Summary of the diagnostic evidence

Table 3: Clinical evidence summary: diagnostic accuracy for signs and symptoms

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
More than 1 attack of acute arthritis							
1 cross-sectional study	82	serious[a]	not serious	not serious	serious[b]	Sensitivity=0.87 (0.69 to 0.96)	LOW
		serious[a]	not serious	not serious	very serious[b]	Specificity=0.17 (0.08 to 0.30)	VERY LOW
Maximum inflammation developed within 1 day							
1 cross-sectional study	82	serious[a]	not serious	not serious	serious[b]	Sensitivity=0.82 (0.63 to 0.94)	VERY LOW
		serious[a]	not serious	not serious	very serious[b]	Specificity=0.40 (0.26 to 0.55)	VERY LOW
Monoarthritis attack							
1 cross-sectional study	82	serious[a]	not serious	not serious	serious[b]	Sensitivity=0.86 (0.68 to 0.96)	LOW
		serious[a]	not serious	not serious	very serious[b]	Specificity=0.24 (0.13 to 0.37)	VERY LOW
Erythema							
1 cross-sectional study	82	serious[a]	not serious	not serious	serious[b]	Sensitivity=0.72 (0.53 to 0.87)	LOW
		serious[a]	not serious	not serious	very serious[b]	Specificity=0.58 (0.43 to 0.72)	VERY LOW
First MTP joint painful or swollen							
1 cross-sectional study	82	serious[a]	not serious	not serious	serious[b]	Sensitivity=0.83 (0.65 to 0.94)	LOW
		serious[a]	not serious	not serious	serious[b]	Specificity=0.69 (0.54 to 0.81)	LOW
Unilateral first MTP joint attack							
1 cross-sectional study	82	serious[a]	not serious	not serious	serious[b]	Sensitivity=0.77 (0.58 to 0.90)	LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
		serious[a]	not serious	not serious	serious[b]	Specificity=0.71 (0.56 to 0.83)	LOW
Unilateral tarsal joint attack							
1 cross-sectional study	82	serious[a]	not serious	not serious	very serious[b]	Sensitivity=0.48 (0.29 to 0.67)	VERY LOW
		serious[a]	not serious	not serious	serious[b]	Specificity=0.78 (0.64 to 0.88)	LOW
Tophus (proven or suspected)							
1 cross-sectional study	82	serious[a]	not serious	not serious	very serious[b]	Sensitivity=0.37 (0.19 to 0.58)	VERY LOW
		serious[a]	not serious	not serious	not serious	Specificity=0.98 (0.87 to 1.00)	MODERATE
Painful joint swelling. Abrupt onset, clearing in 1-2 weeks initially							
1 cross-sectional study	82	serious[a]	not serious	not serious	serious[b]	Sensitivity=0.70 (0.50 to 0.86)	LOW
		serious[a]	not serious	not serious	very serious[b]	Specificity=0.61 (0.46 to 0.74)	VERY LOW
Started at night							
1 cross-sectional study	82	serious[a]	not serious	not serious	serious[b]	Sensitivity=0.90 (0.70 to 0.99)	LOW
		serious[a]	not serious	not serious	serious[b]	Specificity=0.48 (0.32 to 0.63)	LOW

a Risk of bias was assessed using the QUADAS-II checklist. Evidence quality was downgraded by 1 increment if the evidence was at high risk of bias, and downgraded by 2 increments if the evidence was at very high risk of bias. Unclear if it was every patient that had synovial fluid aspiration that was selected for inclusion. No details of time between joint aspiration (reference test) and index test.

b The evidence was downgraded by one increment if the 95% confidence interval crossed one clinical decision threshold and by two increments if it crossed two clinical decision thresholds. The GC set the thresholds for sensitivity and specificity as 50% (no better than chance) and 80% (threshold to recommend a test).

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

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

See also the health economic study selection flow chart in Appendix F.

1.1.8 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.9 Evidence statements

Clinical evidence statements

Economic.

- No relevant economic evaluations were identified.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

Diagnostic accuracy of individual signs and symptoms for diagnosing gout was the outcome prioritised for this review. Sensitivity was considered the most important measure by the Guideline Committee for this review question because most patients are treated in primary care where less testing, such as imaging or joint aspiration is performed and may be feasible. The consequences of missing a diagnosis would mean treatment for gout would be delayed for the patient. Specificity of the signs and symptoms was also deemed important to identify those with gout as they will be treated for life. An incorrect diagnosis could be detrimental to the person's health and could be an ongoing cost until this was identified.

1.1.10.2 The quality of the evidence

Only one small study was identified for the diagnostic accuracy of signs and symptoms for gout. The committee took into account the quality of the outcomes (moderate to very low across outcomes), which was reduced due to potential biases, according to the QUADAS-2 assessment, due to lack of clarity on the selection of patients for inclusion in the study and the time between the reference and index test. The quality was further reduced by imprecision of the sensitivity and specificity. The committee thought that although the evidence was limited, and the quality was low the sensitivity and specificity of the signs and symptoms reported were generally in line with their experience in clinical practice. The committee agreed that a person having only one sign or symptom was not enough to make a diagnosis of gout, unless the person has tophi, but a person presenting with a combination of symptoms or signs would be a good clinical indication of gout.

The committee were interested in evidence for people with pre-existing osteoarthritis, because gout more commonly occurs in joints affected by osteoarthritis, and this can lead to diagnostic uncertainty. A separate stratum for this population was included to see if there

was any evidence to aid diagnosing specifically in people with OA, however, none was identified.

1.1.10.3 Benefits and harms

The committee discussed the clinical evidence presented and noted the sensitivity and specificity for the individual signs and symptoms of gout ranged from 0.37 to 0.90 and 0.17 to 0.98 respectively. A threshold had been agreed a priori of 0.80 for sensitivity and specificity for recommending a sign/symptom and 0.50 would indicate no clinical benefit, however none of the evidence met these thresholds for both sensitivity and specificity. Over 0.80 sensitivity was found for: having more than 1 attack (flare) of acute arthritis; maximum inflammation developing within 1 day; monoarthritis attack; first MTP joint being painful or swollen and starting at night, however all of the confidence intervals crossed this threshold. Specificity over 0.80 was found for tophus (proven or suspected) and the confidence interval did not cross the threshold. The first MTP joint being painful or swollen had adequate sensitivity (0.83) and specificity of 0.69 and unilateral first MTP joint attack had sensitivity of 0.77 and specificity of 0.71, which were considered close to the thresholds, however the confidence intervals were very wide and crossed the threshold. These were taken into consideration for the recommendations, however the committee noted that in clinical practice, a person presenting with only one individual sign or symptom may not be indicative of gout. The committee acknowledged that there is typically high suspicion of gout if a person presents with rapid onset of pain, redness, and swelling of the first metatarsophalangeal (MTP) joint(s), especially if symptom onset occurs overnight. In addition, if a person presents with tophi this would usually be indicative of gout which has been untreated for a prolonged period of time. If the symptoms listed above present in other joints (such as the knee, wrist, ankle, mid-foot joints, finger interphalangeal joints or elbow), these may be signs and symptoms of gout.

The committee concluded that the signs and symptoms identified in the clinical review are typical of what people with gout experience. It was noted that gout can be diagnosed with confidence if rapid onset (often overnight) of severe pain, redness and swelling affects the first MTP joint. However, when a person presents with a painful, red, swollen joint, other diagnoses should be considered first for example, septic arthritis, calcium pyrophosphate crystal deposition or inflammatory arthritis. Septic arthritis is a medical emergency and if suspected the person should be referred immediately, according to the local care pathway. It was also noted that although gout is most commonly monoarticular, polyarticular presentations are possible, particularly in people with CKD. The committee noted that gout and other forms of arthritis can be extremely painful, so it is imperative people are given appropriate medication to alleviate the pain before further diagnostic tests are undertaken

The committee noted no evidence had been found relating specifically to diagnosing in people with pre-existing osteoarthritis and in this population, the clinician would take into account the person's history, symptoms, signs and serum urate levels, and may need to consider other diagnostic tests to diagnose gout.

As the evidence was limited the committee used their clinical expertise of current practice, alongside the findings from the study, to make the recommendations.

1.1.10.4 Cost effectiveness and resource use

No economic evaluations were identified for this review question.

Overall, the committee made recommendations in line with the signs and symptoms people with gout typically present with in clinical practice. Therefore, this recommendation is not expected to result in a substantial resource impact.

1.1.10.5 Other factors the committee took into account

The committee agreed that the majority of patients will be treated in primary care, but recommendations must also be suitable for secondary care.

These recommendations link to those from the diagnostic approaches for gout review. This review relates to first presentation of the person with suspected gout, where diagnosis is typically made by taking the history and examination of the patient and measuring the serum urate level. Clinical history and serum urate tests are investigated for their diagnostic accuracy in the diagnostic approaches review which also includes further diagnostic approaches which may subsequently conducted such as radiography, ultasonography against the gold standard of joint aspiration of synovial fluid.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.1 to 1.1.5

1.1.12 References

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Appendices

Appendix A – Review protocols

Review protocol for what signs and symptoms indicate gout as a possible diagnosis?

ID	Field	Content
0.	PROSPERO registration number	Not applicable
1.	Review title	What signs and symptoms indicate gout as a possible diagnosis?
2.	Review question	What signs and symptoms indicate gout as a possible diagnosis?
3.	Objective	To determine what signs and symptoms should prompt a healthcare professional to suspect gout, and consider further investigation.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details) Searches will be restricted by: • English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Gout (including people with gout and chronic kidney disease)
6.	Population	Inclusion: Adults (18 years and older) with suspected gout

		Strata: People with pre-existing osteo-arthritis Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout
7.	Signs and symptoms	• Distribution of affected joints (monoarticular /polyarticular involvement, which joints e.g first metatarsophalangeal joint) • Previous episodes of similar acute arthritis • Rapid onset of severe pain • Rapid onset of swelling • Erythema • Joint tenderness • Tophi • Overnight onset (nocturnal onset) • Combinations of the above
8.	Reference standard	Confirmed diagnosis of gout by various means: • Joint aspiration (urate crystals are observed in synovial fluid or tophi) is the gold standard. • X-ray • Ultrasound • Dual-energy CT (DECT) The reference standards would be analysed separately.
9.	Types of study to be included	Diagnostic accuracy review: • Diagnostic accuracy cross-sectional studies. • Systematic reviews of diagnostic accuracy cross-sectional studies. If no diagnostic accuracy studies are found, we will look for diagnostic association studies: • Association data: ○ Adjusted RR or OR (adjusted for key confounders of age or gender)
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.

		• Case-control studies will be excluded
11.	Context	In clinical practice it is important for signs and symptoms of gout to be identified so the person with suspected gout can be referred for further investigations or so that management of gout can be initiated.
12.	Primary outcomes (critical outcomes)	Diagnostic accuracy review: Primary paired outcome: • Sensitivity/specificity
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). A standardised form will be used to extract data from studies (see manual QUADAS-2 will be used to assess the quality of diagnostic accuracy studies. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. The

		appropriate checklist for this review is QUADAS-2.
16.	Strategy for data synthesis	: • Coupled forest plots of sensitivity and specificity with their 95% CI across studies will be produced for each test (and for each clinically relevant threshold), using RevMan5. . Data would be meta-analysed when data are available from 3 or more studies (given data were reported at the same threshold or within a defined range of similar thresholds). To do this, data would be entered into a bivariate model using WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software. For diagnostic association review: • Aggregate data on diagnostic association of signs and symptoms will be collected and synthesised in a quantitative data analysis. • If more than one study covered the same combination of population, sign/symptom, outcome and confounding factors accounted for then meta-analysis will be used to pool results. Meta-analysis will be carried out suing the generic inverse variance function on Review Manager using fixed effect model. Data synthesis will beo completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer. • Data from the meta-analysis will be presented and quality assessed in adapted GRADE tables taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each sign/symptom. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect

<table>
<tr><td></td><td></td><td colspan="3">estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.
• If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.
Publication or other bias will only be taken in to consideration in the quality assessment if it is apparent.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Subgroups that will be investigated if heterogeneity is present:
• None</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☐</td><td colspan="2">Intervention</td></tr>
<tr><td>☒</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">5th May 2021</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">13th June 2022</td></tr>
<tr><td rowspan="8">23.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☐</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>

24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail managementofgout@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre
25.	Review team members	From the National Guideline Centre: Gill Ritchie [Guideline lead] Julie Neilson [Senior systematic reviewer] Audrius Stonkus [Systematic reviewer] Alexandra Bonnon [Health economist] Amber Hernaman [Project manager] Joseph Runicles [Information specialist]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If

		extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]	
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. [Add in any additional agree dissemination plans.]	
32.	Keywords	[Give words or phrases that best describe the review.]	
33.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health 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 health 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	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005 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 H of Developing NICE guidelines: the manual (2014).[37] **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. A health economic evidence table will be completed and it will be included in the health 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 a health economic evidence table will not be completed and it will not be included in the health 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 guideline committee if required. The ultimate aim is to include health 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 in the excluded health economic studies appendix below. 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 be excluded before being assessed for applicability and methodological limitations. *Health 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 be 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 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match 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

- What signs and symptoms indicate gout as a possible diagnosis?
- What are the most accurate and cost-effective approaches to diagnosing gout, in particular serum urate level compared with joint aspiration?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[37]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 06 July 2021	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (animal studies, letters, comments)
Embase (OVID)	1974 – 06 July 2021	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (animal studies, letters, comments)

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.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.	randomized controlled trial.pt.
28.	controlled clinical trial.pt.
29.	randomi#ed.ti,ab.
30.	placebo.ab.
31.	randomly.ti,ab.
32.	Clinical Trials as topic.sh.
33.	trial.ti.
34.	or/27-33
35.	Meta-Analysis/
36.	exp Meta-Analysis as Topic/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(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.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	Epidemiologic studies/
47.	Observational study/
48.	exp Cohort studies/
49.	(cohort adj (study or studies or analys* or data)).ti,ab.
50.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
51.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
52.	Controlled Before-After Studies/

53.	Historically Controlled Study/
54.	Interrupted Time Series Analysis/
55.	(before adj2 after adj2 (study or studies or data)).ti,ab.
56.	exp case control studies/
57.	case control*.ti,ab.
58.	Cross-sectional studies/
59.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
60.	or/46-59
61.	(predictive value* or PPV or NPV).ti,ab.
62.	likelihood ratio*.ti,ab.
63.	likelihood function/
64.	((area under adj4 curve) or AUC).ti,ab.
65.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
66.	gold standard.ab.
67.	exp Diagnostic errors/
68.	(false positiv* or false negativ*).tw.
69.	Diagnosis, Differential/
70.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
71.	or/61-70
72.	26 and (34 or 45 or 60 or 71)

Embase (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.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.	random*.ti,ab.
26.	factorial*.ti,ab.
27.	(crossover* or cross over*).ti,ab.
28.	((doubl* or singl*) adj blind*).ti,ab.
29.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
30.	crossover procedure/
31.	single blind procedure/
32.	randomized controlled trial/
33.	double blind procedure/
34.	or/25-33
35.	systematic review/
36.	meta-analysis/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(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.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	Clinical study/
47.	Observational study/
48.	family study/
49.	longitudinal study/
50.	retrospective study/
51.	prospective study/
52.	cohort analysis/
53.	follow-up/
54.	cohort*.ti,ab.
55.	53 and 54
56.	(cohort adj (study or studies or analys* or data)).ti,ab.
57.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
58.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
59.	(before adj2 after adj2 (study or studies or data)).ti,ab.
60.	exp case control study/
61.	case control*.ti,ab.
62.	cross-sectional study/

63.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
64.	or/46-52,55-63
65.	exp "sensitivity and specificity"/
66.	(sensitivity or specificity).ti,ab.
67.	((pre test or pretest or post test) adj probability).ti,ab.
68.	(predictive value* or PPV or NPV).ti,ab.
69.	likelihood ratio*.ti,ab.
70.	((area under adj4 curve) or AUC).ti,ab.
71.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
72.	diagnostic accuracy/
73.	diagnostic test accuracy study/
74.	gold standard.ab.
75.	exp diagnostic error/
76.	(false positiv* or false negativ*).ti,ab.
77.	differential diagnosis/
78.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
79.	or/65-78
80.	24 and (34 or 45 or 64 or 79)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Gout population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018). 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 and quality of life studies.

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 14 June 2021 Quality of Life 1946 – 14 June 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments)
Embase	Health Economics 1 January 2014 – 14 June 2021 Quality of Life 1974 – 14 June 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments)
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	Uric Acid/
5.	uric acids*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.
7.	hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.
9.	podagra.ti,ab.
10.	or/1-9
11.	letter/
12.	editorial/
13.	news/
14.	exp historical article/
15.	Anecdotes as Topic/
16.	comment/
17.	case report/
18.	(letter or comment*).ti.
19.	or/11-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	10 not 28
30.	limit 29 to English language
31.	Economics/
32.	Value of life/
33.	exp "Costs and Cost Analysis"/
34.	exp Economics, Hospital/
35.	exp Economics, Medical/
36.	Economics, Nursing/
37.	Economics, Pharmaceutical/
38.	exp "Fees and Charges"/
39.	exp Budgets/
40.	budget*.ti,ab.

41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/31-46
48.	quality-adjusted life years/
49.	sickness impact profile/
50.	(quality adj2 (wellbeing or well being)).ti,ab.
51.	sickness impact profile.ti,ab.
52.	disability adjusted life.ti,ab.
53.	(qal* or qtime* or qwb* or daly*).ti,ab.
54.	(euroqol* or eq5d* or eq 5*).ti,ab.
55.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
56.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
57.	(hui or hui1 or hui2 or hui3).ti,ab.
58.	(health* year* equivalent* or hye or hyes).ti,ab.
59.	discrete choice*.ti,ab.
60.	rosser.ti,ab.
61.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
62.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
63.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
64.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
65.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
66.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
67.	or/48-66
68.	30 and (47 or 67)

Embase (Ovid) search terms

1.	exp gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	exp uric acid/
5.	uric acid*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.
7.	exp hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.
9.	podagra.ti,ab.
10.	or/1-9
11.	letter.pt. or letter/
12.	note.pt.

13.	editorial.pt.
14.	Case report/ or Case study/
15.	(letter or comment*).ti.
16.	or/11-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	Nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental animal/
23.	Animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	10 not 26
28.	limit 27 to English language
29.	health economics/
30.	exp economic evaluation/
31.	exp health care cost/
32.	exp fee/
33.	budget/
34.	funding/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/29-41
43.	quality adjusted life year/
44.	"quality of life index"/
45.	short form 12/ or short form 20/ or short form 36/ or short form 8/
46.	sickness impact profile/
47.	(quality adj2 (wellbeing or well being)).ti,ab.
48.	sickness impact profile.ti,ab.
49.	disability adjusted life.ti,ab.
50.	(qal* or qtime* or qwb* or daly*).ti,ab.
51.	(euroqol* or eq5d* or eq 5*).ti,ab.
52.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
53.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
54.	(hui or hui1 or hui2 or hui3).ti,ab.
55.	(health* year* equivalent* or hye or hyes).ti,ab.
56.	discrete choice*.ti,ab.
57.	rosser.ti,ab.

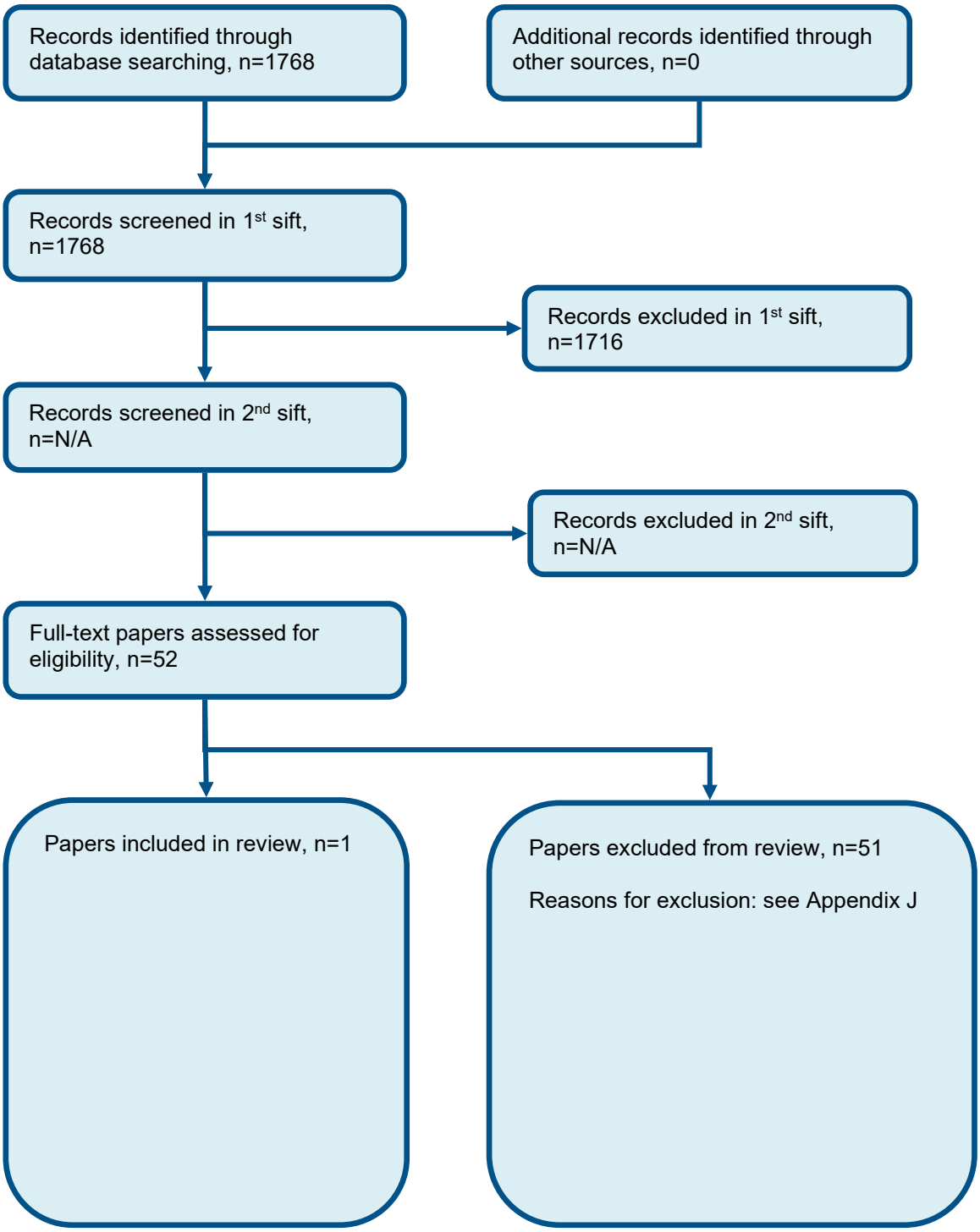
58.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
59.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
60.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
61.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
62.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
63.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
64.	or/43-63
65.	28 and (42 or 64)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Gout EXPLODE ALL TREES
#2.	(gout*)
#3.	(toph*)
#4.	MeSH DESCRIPTOR Uric Acid EXPLODE ALL TREES
#5.	(uric acid*)
#6.	((urate near (crystal* or sodium or mono sodium)))
#7.	MeSH DESCRIPTOR Hyperuricemia EXPLODE ALL TREES
#8.	((hyperuric* or hyper uric*))
#9.	(podagra)
#10.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

Appendix C –Diagnostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of signs and symptoms for diagnosing gout



Appendix D –Diagnostic evidence

Reference	**Malik 2009[35]**
Study type	Diagnostic accuracy study
Study methodology	Data source: participants were interviewed and charts reviewed after completion of the interviews for presence of hyperuricemia, tophi, x-rays showing asymmetric swelling within a joint or subcortical cysts without erosions, and joint fluid culture negative for organisms during an attack. Responses were recorded and evaluated for whether the clinical features of ARA (ACR), Rome, or NY criteria for gout were met. The results of the clinical aspects of the criteria were then compared with crystal analysis for definitive gout diagnosis. Recruitment: participants who were seen in the Department of Veterans Affairs rheumatology clinic were selected if they had had synovial fluid aspirated and analysed at some time with compensated light microscopy.
Number of patients	n = 82
Patient characteristics	Age, mean (SD): 64.5 years Gender (male to female ratio): 77:5 Ethnicity: 56 (69%) African American; 25 (30%) white; 1 (1%) Hispanic/Latino. Setting: Department of Veterans Affairs rheumatology clinic, Philadelphia, Pennsylvania. Country: USA 30 patients had MSU crystals identified in joint aspirations and 52 did not. 21 had CPPD crystals, 3 had apatite crystals, and 28 had no crystals identified. Inclusion criteria: Patients at the clinic who had had synovial fluid aspirated and analysed at some time with compensated polarized light microscopy; any patients with suspected diagnosis with and without monosodium urate (MSU) crystal presence in their joint fluid. Confirmation of crystal presence was by 2 persons experienced in laboratory examination of joint fluids. The majority of patients (75.6%) had an aspiration of the knee joint although metatarsophalangeal (MTP), wrist, elbow, ankle and proximal interphalangeal (PIP) joints were also sources of some synovial fluids. Exclusion criteria: patients with questions not asked or with results not available were excluded. .
Target condition(s)	Gout

Reference	**Malik 2009[35]**				
Index test(s) and reference standard	Index tests: Clinical features of ARA (ACR), Rome or NY criteria for gout. All subjects were asked whether they had each of the clinical features of the 3 sets of proposed criteria for gout at any time. Patients were not examined by the questioner. The interviewer was blinded to the results of the synovial fluid analysis. Charts were reviewed after completion of the interviews for the presence of hyperuricemia (defined as serum urate greater than 6.8mg/dl), tophi (proven or suspected), x-rays showing asymmetric swelling within a joint or subcortical cysts without erosions, and joint fluid culture negative for organisms during an attack. Responses were recorded and evaluated for whether the clinical features of ARA (ACR), Rome, or NY criteria for gout were met. The results of the clinical aspects of the criteria were then compared with crystal analysis for definitive gout diagnosis. Reference standard: joint aspiration of synovial fluid Gout was defined by: confirmation of urate crystal presence. Time between measurement of index test and reference standard:				
2×2 table More than 1 attack of acute arthritis		Reference standard +	Reference standard −	Total	TP = True positive FN = False negative FP = False positive TN = True negative
	Index test +	26 TP	43 FP	69	
	Index test −	4 FN	9 TN	13	
	Total	30	52	82	
2×2 table maximum inflammation developed within 1 day		Reference standard +	Reference standard −	Total	
	Index test +	23 TP	30 FP	43	An error was in the paper: FP was reported as 20 rather than 30.
	Index test −	5 FN	20 TN	25	
	Total	28	40	68	
2×2 table monoarthritis attack		Reference standard +	Reference standard −	Total	
	Index test +	25 TP	39 FP	64	
	Index test −	4 FN	12 TN	16	
	Total	29	51	80	
2×2 table Erythema		Reference standard +	Reference standard −	Total	
	Index test +	21 TP	20 FP	41	
	Index test −	8 FN	28 TN	36	
	Total	29	48	77	
2×2 table		Reference standard +	Reference standard −	Total	

Reference	**Malik 2009[35]**				
first MTP joint painful or swollen	Index test +	25 TP	16 FP	41	
	Index test −	5 FN	35 TN	40	
	Total	30	51	81	
2×2 table unilateral first MTP joint attack		Reference standard +	Reference standard −	Total	
	Index test +	23 TP	15 FP	38	
	Index test −	7 FN	36 TN	43	
	Total	30	51	81	
2×2 table unilateral tarsal joint attack		Reference standard +	Reference standard −	Total	
	Index test +	14 TP	11 FP	25	
	Index test −	15 FN	39 TN	54	
	Total	29	50	79	
2×2 table tophus (proven or suspected)		Reference standard +	Reference standard −	Total	
	Index test +	10 TP	1 FP	11	
	Index test −	17 FN	41 TN	58	
	Total	27	42	69	
2×2 table painful joint swelling. Abrupt onset, clearing in 1-2 week initially		Reference standard +	Reference standard −	Total	
	Index test +	19 TP	20 FP	39	
	Index test −	8 FN	31 TN	39	
	Total	27	51	78	
2x2 table started at night		Reference standard +	Reference standard −	Total	
	Index test +	19 TP	23 FP	42	
	Index test −	2 FN	21 TN	23	
	Total	21	44	65	

Reference	Malik 2009[35]
Statistical measures	Sign/symptom: more than 1 attack of acute arthritis Sensitivity 87% (95% CI 69% to 96%) Specificity 17% (95% CI 8% to 30%) Sign/symptom: maximum inflammation developed within 1 day Sensitivity 82% (95% CI 63% to 94%) Specificity 40% (95% CI 26% to 55%) Sign/symptom: monoarthritis attack Sensitivity 86% (95% CI 68% to 96%) Specificity 24% (95% CI 13% to 37%) Sign/symptoms: erythema Sensitivity 72% (95% CI 53% to 87%) Specificity 58% (95% CI 43% to 72%) Sign/symptoms: first MTP joint painful or swollen Sensitivity 83% (95% CI 65% to 94%) Specificity 69% (95% CI 54% to 81%) Sign/symptoms: unilateral first MTP joint attack Sensitivity 77% (95% CI 58% to 90%) Specificity 71% (95% CI 56% to 83%) Sign/symptoms: unilateral tarsal joint attack Sensitivity 48% (95% CI 29% to 67%) Specificity 78% (95% CI 64% to 88%) Sign/symptoms: tophus (proven or suspected) Sensitivity 37% (95% CI 19% to 58%) Specificity 98% (95% CI 87% to 100%) Sign/symptoms: painful joint swelling. Abrupt onset, clearing in 1-2 week initially. Sensitivity 70% (95% CI 50% to 86%) Specificity 61% (95% CI 46% to 74%)

Reference	Malik 2009[35]
	Sign/symptoms: started at night Sensitivity 90% (95% CI 70% to 99%) Specificity 48% (95% CI 32% to 63%)
Source of funding	Not reported
Limitations	Unclear if it was every patient that had synovial fluid aspiration that was selected for inclusion. No details of time between joint aspiration (reference test) and index test.
Comments	The paper mis-reported 20 rather than 30 for maximum inflammation developed within 1 day, but numbers were worked out by sensitivity and specificity reported.

Appendix E – Forest plots

E.1 Coupled sensitivity and specificity forest plots

Figure 2: Sensitivity and specificity of >1 attack of arthritis for diagnosing gout

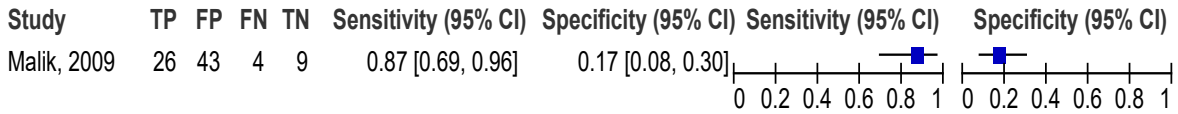


Figure 3: Sensitivity and specificity of maximum inflammation developed within 1 day for diagnosing gout

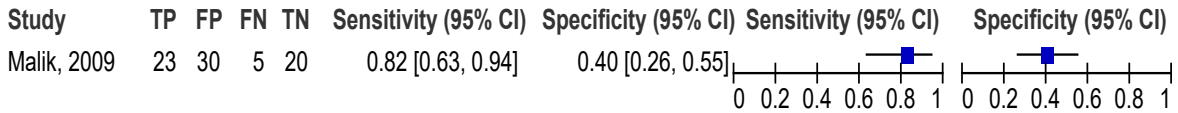


Figure 4: Sensitivity and specificity of monoarthritis attack for diagnosing gout

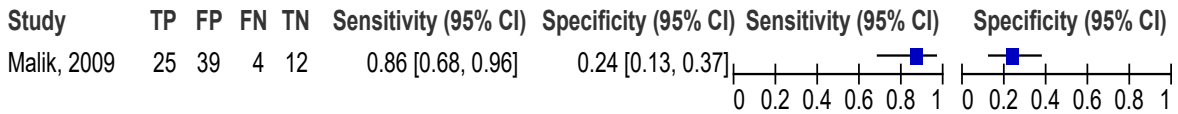


Figure 5: Sensitivity and specificity of erythema for diagnosing gout

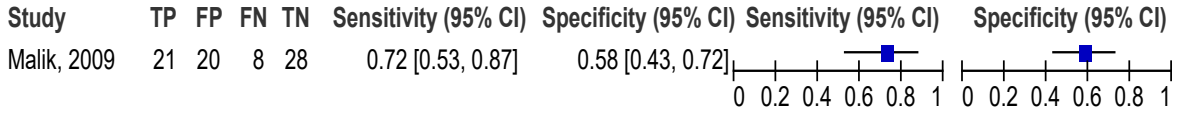


Figure 6: Sensitivity and specificity of first MTP joint painful or swollen for diagnosing gout

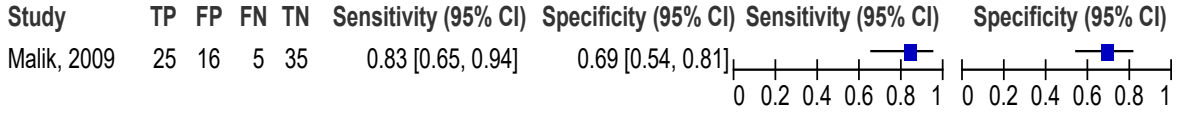


Figure 7: Sensitivity and specificity of unilateral first MTP joint attack for diagnosing gout

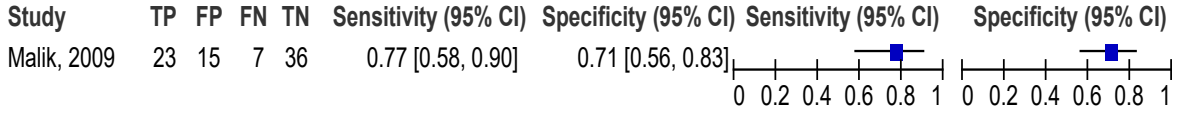


Figure 8: Sensitivity and specificity of unilateral tarsal joint attack for diagnosing gout

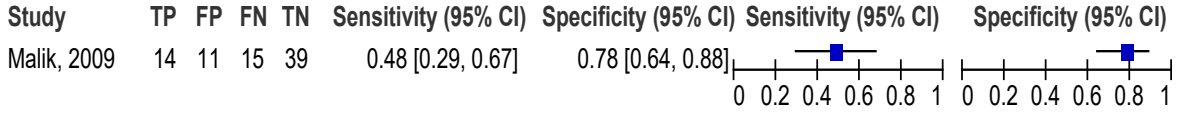


Figure 9: Sensitivity and specificity of tophus (proven or suspected) for diagnosing gout

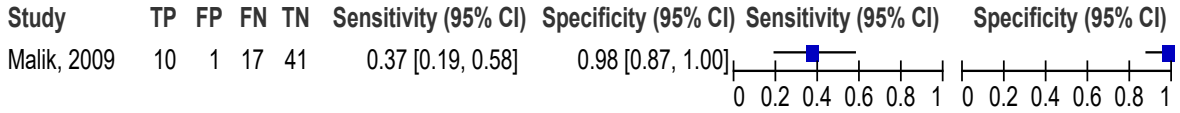


Figure 10: Sensitivity and specificity of painful joint swelling. Abrupt onset, clearing in 1-2 weeks initially for diagnosing gout

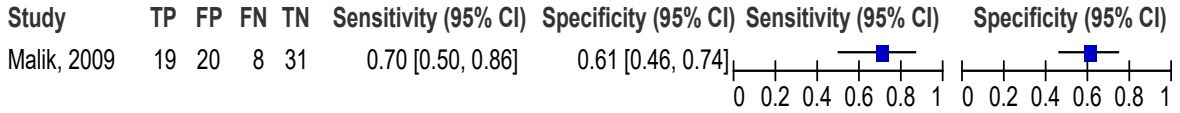
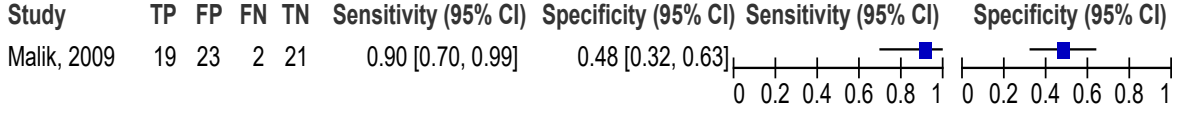


Figure 11: Sensitivity and specificity of started at night for diagnosing gout

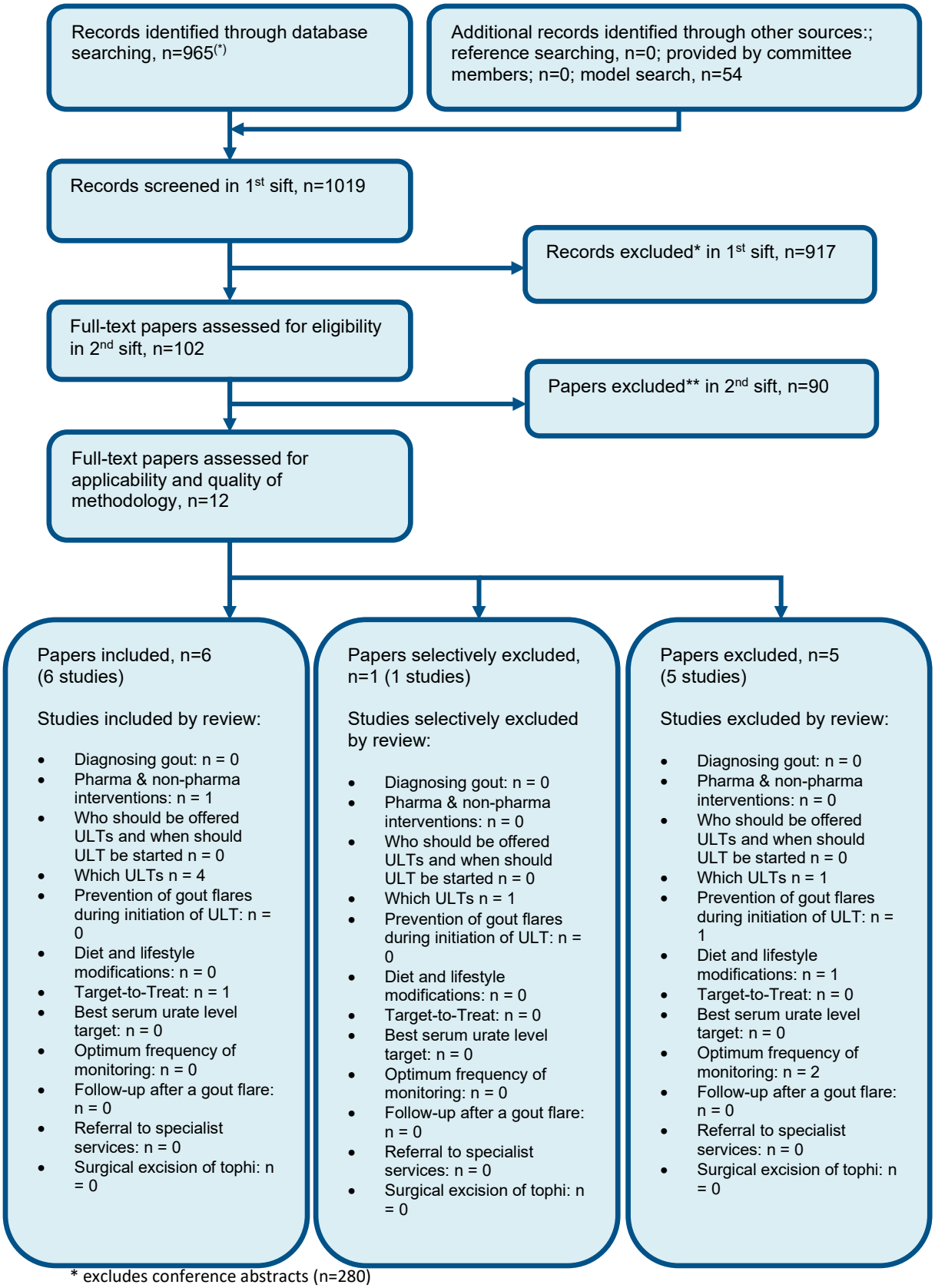


E.2 ROC curves

Meta-analysis was not possible as only one diagnostic accuracy study was found for this review question, therefore no ROC curves were produced.

Appendix F – Economic evidence study selection

Figure 12: Flow chart of health economic study selection for the guideline



* excludes conference abstracts (n=280)

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

Appendix G – Economic evidence tables

None.

Appendix H – Health economic model

No original economic modelling was undertaken for this review question.

Appendix I – Excluded studies

Clinical studies

Table 6: Studies excluded from the clinical review

Reference	Reason for exclusion
Abhishek 2016[1]	Incorrect study design: case-control study
Aune 2014[2]	Systematic review and dose-response meta-analysis, did not match the protocol
Azab 2020[3]	Incorrect study design: case-control study
Bardin 2014[4]	Incorrect study design: abstract
Bhole 2010[5]	Incorrect study design: not diagnostic accuracy but a risk factor study
Cea Soriano 2011[6]	Incorrect study design: nested case-control study
Chen 2020[7]	Incorrect study design: case-control study
Choi 2019[8]	Incorrect index test: classification criteria
Chouk 2019 [9]	Incorrect index test: serum procalcitronin levels
Chung 2010[10]	Incorrect study design: not a diagnostic accuracy study but a risk factor study
Dao 2010[11]	Incorrect study design: case-control study
Dehlin 2015[13]	Incorrect index test: classification criteria
Dehlin 2019[12]	Incorrect index test: classification criteria
Eisenberg 1984[14]	Incorrect index test: assessing synovial fluid analysis
Expert Panel 2017[15]	Incorrect index test: classification criteria
Gamala 2020[16]	Incorrect index test: classification criteria
Giordano 2021[17]	Not English language
Hernandez-Cuevas 2009[18]	Time between first gout attack and diagnosis of metabolic syndrome
Hill 2012[19]	Incorrect study design: abstract
Hou 2019[20]	Incorrect study design: not a diagnostic accuracy study
Janssens 2010[22]	Incorrect index test: ACR-EULAR classification criteria
Janssens 2017[21]	Incorrect index test: classification criteria
Jatuworapruk 2016[23]	Unable to extract 2x2 table from the information provided.
Kienhorst 2014[25]	Unable to extract 2x2 table from the information provided.
Kienhorst 2015[24]	Incorrect study design: classification criteria validation study
Krishnan 2012[26]	Incorrect study design: not a diagnostic accuracy study
Kumar 2012[27]	Incorrect study design: not a diagnostic accuracy study but a risk factor study
Lenski 2014[28]	Incorrect index test: serum markers
Liang 2020[29]	Incorrect study design: case-control study
Lin 2000[30]	Incorrect study design: not a diagnostic accuracy study
Lin 2013[32]	Incorrect study design: not a diagnostic accuracy study
Lin 2018[31]	Systematic review and meta-analysis, did not match the protocol

Reference	Reason for exclusion
Lin 2000[30]	Incorrect study design: not a diagnostic accuracy study but a risk factor study
Louthrenoo 2017[33]	Incorrect index test: classification criteria
Lu 2019[34]	Incorrect study design: not a diagnostic accuracy study
Mohd 2011 [36]	Incorrect study design: case series study
Neogi 2015[38]	Incorrect index test: classification criteria
Park 2014[39]	Incorrect index test: crystal identification
Poh 2011[40]	Incorrect index test: MRI features
Rigby 1994[41]	Incorrect index test: classification criteria
Rothenbacher 2011[42]	Incorrect study design: not a diagnostic accuracy but a risk factor study of gout flares
Shen 2021[43]	Incorrect index test: biomarkers
Sun 2019[44]	Incorrect index test: diagnostic accuracy of ultrasound
Taylor 2015 [46]	Incorrect study design: not a diagnostic accuracy study
Taylor 2016[45]	Incorrect index test: classification criteria
Vasquez-Mellado 2012[47]	Unable to extract 2x2 table from the information provided.
Wang 2015[48]	Incorrect study design: CKD as a risk factor
Wang 2015[49]	Incorrect study design: cigarette smoking as a risk factor
Westerfield 2016[50]	Incorrect index test: classification criteria
Zhang 2006[51]	Incorrect study design: literature review of various study designs
Zhang 2020[52]	Incorrect study design: not a diagnostic accuracy study

Health Economic studies

None.