National Institute for Health and Care Excellence

Guideline version (Final)

Gout: diagnosis and management

[C] Evidence reviews for what are the most accurate and cost-effective approaches to diagnosing gout, in particular serum urate level compared with joint aspiration?

NICE guideline NG219

Evidence reviews underpinning recommendations 1.1.7 to 1.1.9 in the NICE guideline

June 2022

Final

National Institute for Health and Care Excellence

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1.1 Review question: What are the most accurate and cost-effective approaches to diagnosing gout, in particular serum urate level compared with joint aspiration?

1.1.1 Introduction

In the UK, 95-99% of people with gout have their diagnosis made in primary care following an acute presentation via a detailed history and examination of the affected joint(s). Clinical diagnosis is subsequently confirmed with the use of a clinical investigation.

Currently, the investigation of choice in primary care is a serum urate level. Where there is diagnostic uncertainty, a person may be referred to rheumatology services, where in addition to serum urate levels, joint aspiration and other diagnostic imaging investigations are more likely to be performed. This evidence review evaluates the diagnostic accuracy of the different approaches to diagnosing gout.

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. Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout
Target condition	Gout (including people with gout and chronic kidney disease)
Index tests	• Clinical assessment (history and examination) • Serum urate level (persistently above 380 micromol/L) • Clinical assessment plus serum urate level (history and examination plus serum urate level persistently above 380 micromol/L) • X-ray • Ultrasound • Dual-energy CT (DECT)
Reference standard	Joint aspiration (urate crystals are observed in synovial fluid or tophi)
Statistical measures	Primary paired outcome: Sensitivity/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 accuracy of diagnostic approaches for identifying gout. No studies were found for clinical assessment or serum urate level. Nine studies were included in the review. Ahmad, 2016,[1] Christiansen 2021,[17] Elsaman 2016,[24] Glazebrook 2011,[31] Lamers-Karnebeck 2014,[44] Loffler 2015,[50] Ogdie 2017,[61] Pattamapaspong 2017[65] and Singh 2021.[75] One study included radiography, 3 studies investigated DECT and 7 studies included ultrasound. Particular ultrasound features (images produced from the ultrasound waves) are associated with gout, such as snow-storm sign, double contour (DC) sign and tophi. The sensitivity and the specificity of the ultrasound features (determined by the individual studies) were investigated.

The studies are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below in Table 3 and references in 1.1.13 References . 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 and both being equally important. The committee set clinical decision thresholds as sensitivity/specificity of 0.8 above which a test would be recommended and 0.5 below which a test is of no clinical use.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix I.

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	Index test	Reference standard	Comments
Ahmad 20161	Patients suspected of having gout N=90 Age: median (range): 44 (21-75 years) Gender: 97M/ 3F Country: India	Gout	Radiographs (morphological characteristics) Dual-energy CT (DECT): gout diagnosed by a positive finding of uric acid crystals in a single joint. Bilateral feet and knees scanned.	Joint aspiration of synovial fluid analysis: negatively bifringent uric acid crystals Most severely affected joint	73% of patients were in the acute stage Also used joint aspiration plus ACR criteria as reference standard (not reported) Non-contrast CT accuracy also tested (not reported).
Christiansen 202117	Clinically suspected gout N=82 Age: mean (range): 62.4 (19-88 years) Gender: 70M/ 12F Country: Denmark	Gout	Ultrasound scan (joints and tendons binarily evaluated)	Joint aspiration of synovial fluid analysis	Also used 2015 ACR/EULAR gout classification criteria as a gold standard (not reported).
Elsaman 201624	Patients with episodic mono or oligoarthritis	Gouty arthritis	Ultrasound scan	Joint aspiration of synovial fluid	Diagnosis based on number of joints, not patients.

Study	Population	Target condition	Index test	Reference standard	Comments
	N=100 Age: mean (range): 53.1 (40-75 years) Gender: 55M/ 45F Country: Egypt		(Knee/ MTP joint). Diagnosis on US based on one or more of the 4 sonographic signs (echogenic foci, erosions, DC signs, tophi)	analysis (knee/ MTP joint)	
Glazebrook 201131	Patients suspected of having gout N=94 Age: mean (range): 62.7 (29-89 years) Gender: 53M/ 41F Country: USA	Gout	Dual-energy CT (DECT) (most symptomatic joint)	Joint aspiration of synovial fluid results	Mainly patients with atypical presentations.
Lamers-Karnebeck 201444	Patients with acute mono or oligoarthritis N=54 Age: mean (range): MSU proven gout group: 63.5 (55.5-69.5 years) Non-MSU proven gout group: 55 (41.8-63.5 years) Gender:	Gout/ MSU arthritis	Ultrasound scan (performed on 6 joints: the joint with arthritis, the contralateral side, and two other joints bilaterally)	Joint aspiration of synovial fluid results	Same observers for some index test and reference standard. Included healthy joints

Study	Population	Target condition	Index test	Reference standard	Comments
	MSU proven gout group: 25M/1F Non-MSU proven gout group: 13M/15F Country: The Netherlands				
Loffler 201550Loffler2015	Acute mono or oligoarthritis N=225 joints Age: mean (range): 64 (18-93 years) Gender (M:F): 1.7:1 Country: Germany	Gout	Ultrasound scan (performed on the affected joint)	Joint aspiration of synovial fluid analysis (affected joint)	Cases are joints, not patients Reference standard was SF analysis according to EULAR recommendations
Ogdie 201761	Differential diagnosis of gout (at least 1 swollen joint) N=824 Age: mean (SD): Cases: 60.2 (14.6 years) Controls: 59.5 (16.0 years) Gender (male): 87% for cases, 54% for controls Country: multiple countries	Gout	Ultrasound scan (performed on 1 or more clinically affected joint, most commonly knees, MTP joints and ankles)	Joint aspiration of synovial fluid analysis	Also reports diagnostic accuracy outcomes for US findings by early/ late disease and by presence/absence of clinical tophus (not reported)

Study	Population	Target condition	Index test	Reference standard	Comments
Pattamapaspong 2017	In-patients with acute arthritis N=89 Age: mean (range): 65 (18-87 years) Gender: 60M/ 29F Country: Thailand	Gout	Ultrasound scan (Only the most inflamed joint was scanned)	Joint aspiration of synovial fluid analysis	Inpatient population
Singh 202175	Patients suspected of having gout/ patients being managed for gout N=147 (48 had joint aspiration performed and were included in the analysis) Overall cohort: Age: mean (SD): 64.7 (14.3 years) Gender (M:F): 127M/ 20F Country: France	Gout	Ultrasound scan (positive criteria not stated but noted ultrasound finding included DC sign and tophus as per OMERACT definitions) DECT (a positive scan for gout was defined as the presence f typical colour coded MSU crystal deposits at articular or periarticular sites from a minimum threshold volume of 0.01cm3 (10mm3 or>2mm diameter)	Joint aspiration of synovial fluid analysis (all knee, apart from 1 ankle and 1 metatarsophalangeal)	55/147 already had a diagnosis of gout Also used 2015 ACR/EULAR gout classification criteria ≥8 as a gold standard (not reported). Also reports diagnostic accuracy of DECT/US combined (either/both diagnosing gout).

See Appendix D for full evidence tables

1.1.6 Summary of the diagnostic evidence

Table 3: Clinical evidence summary: diagnostic test accuracy for radiography

Studies	No of Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Radiography to detect gout							
1 study	55	very serious[a]	not serious	not serious	not serious	Sensitivity 0.27 (0.12 to 0.46)	LOW
		very serious[a]	not serious	not serious	not serious	Specificity 1.00 (0.86 to 1.00)	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.							

Table 4: Clinical evidence summary: diagnostic test accuracy for dual-energy CT (DECT)

Studies	No of Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
DECT to detect gout							
3 studies	134	serious[a]	serious[b]	not serious	serious[c]	Sensitivity=0.95 (0.78-0.99)	VERY LOW
		serious[a]	serious[b]	not serious	very serious[c]	Specificity=0.78 (0.30-0.98)	VERY 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. b Inconsistency was assessed by inspection of the sensitivity and specificity forest plots, using the point estimates and confidence intervals. Particular attention was paid to values above or below 50% (diagnosis based on chance alone) and the 80% threshold set by the GC (the threshold above which would be acceptable to recommend a test). The evidence was downgraded by 1 increment if the individual studies varied across 2 areas (for example 50-80% and 80-100%) and by 2 increments if the individual studies varied across 3 areas. cThe 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). Imprecision was assessed on confidence intervals produced by WinBUGS;							

Particular features can be detected, on the images produced by the high frequency sound waves, in order to diagnose gout with ultrasound. These features, determined by the studies, included: snowstorm (ultrasound lesions with a snowstorm appearance); double contour sign (hyperechoic linear density on the surface of the articular cartilage), tophi (tophaceous deposits with a sugar lump appearance), aggregates (hyperechoic aggregates), erosions, synovial hypertrophy (abnormal hypoechoic); doppler activity, echogenic foci (floating echogenic foci in effusion fluid). This review investigated the diagnostic accuracy of the various features, or combinations of features as the person with suspected gout may have one or a few of these features.

Table 5: Clinical evidence summary: diagnostic test accuracy for Ultrasound

Studies	No of Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
DC sign							
5 studies	1084	serious[a]	not serious	not serious	very serious[c]	Sensitivity= 0.69 (0.46-0.87)	VERY LOW
		serious[a]	not serious	not serious	not serious[c]	Specificity= 0.86 (0.67-0.94)	VERY LOW
Tophi							
5 studies	1082	serious[a]	serious[b]	not serious	serious[c]	Sensitivity= 0.49 (0.24-0.75)	VERY LOW
		serious[a]	serious[b]	not serious	not serious	Specificity= 0.94 (0.85-0.98)	VERY LOW
Aggregates (hyperechoic aggregates)							
2 studies	171	serious[a]	serious[b]	not serious	serious[c]	Sensitivity= 0.58 (0.44 to 0.72)	VERY LOW
		serious[a]	serious[b]	not serious	serious[c]	Specificity= 0.92 (0.78 to 0.98)	VERY LOW
Erosions							
1 study	82	not serious	not serious	not serious	not serious	Sensitivity= 0.77 (0.64, 0.87)	HIGH

Studies	No of Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
		not serious	not serious	not serious	Very serious[c]	Specificity= 0.56 (0.35, 0.76)	LOW
Synovial hypertrophy							
1 study	82	not serious	not serious	not serious	not serious	Sensitivity= 0.98 (0.91, 1.00)	HIGH
		not serious	not serious	not serious	serious[c]	Specificity= 0.08 (0.01, 0.26)	MODERATE
Doppler activity							
1 study	82	not serious	not serious	not serious	serious[c]	Sensitivity= 0.81 (0.68, 0.9)	MODERATE
		not serious	not serious	not serious	very serious[c]	Specificity= 0.44 (0.24, 0.65)	LOW
Diagnosis of gout							
1 study	48	very serious[a]	not serious	not serious	serious[c]	Sensitivity= 0.84 (0.69, 0.94)	VERY LOW
		very serious[a]	not serious	not serious	serious[c]	Specificity= 0.60 (0.26, 0.88)	VERY LOW
Any abnormality (DC sign/ snowstorm/tophi)							
2 studies	868	very serious[a]	serious[b]	serious	serious[c]	Sensitivity= 0.77 (0.73, 0.81)	VERY LOW
		very serious[a]	not serious	not serious	not serious	Specificity= 0.84 (0.80 to 0.88)	VERY LOW
Snowstorm sign							
2 studies	873	very serious[a]	not serious	not serious	serious[c]	Sensitivity= 0.30 (0.26, 0.35)	VERY LOW
		very serious[a]	not serious	not serious	serious[c]	Specificity= 0.91 (0.88, 0.94)	VERY LOW
All 3 features (DC sign/ hyperechoic aggregates/ tophi)							
1 study	89	serious[a]	not serious	not serious	not serious	Sensitivity= 0.17 (0.08, 0.30)	MODERATE

Studies	No of Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
		serious[a]	not serious	not serious	not serious	Specificity= 1.00 (0.9, 1.00)	MODERATE
2 features (DC sign/ snowstorm/ tophi)							
1 study	825	very serious[a]	not serious	not serious	not serious	Sensitivity= 0.44 (0.39, 0.49)	LOW
		very serious[a]	not serious	not serious	not serious	Specificity= 0.95 (0.93, 0.97)	LOW
3 features (DC sign/ snowstorm/ tophi)							
1 study	824	very serious[a]	not serious	not serious	not serious	Sensitivity= 0.14 (0.11, 0.18)	LOW
		very serious[a]	not serious	not serious	not serious	Specificity= 0.98 (0.96, 0.99)	LOW
Any abnormality (DC sign/ hyperechoic aggregates/ tophus)							
1 study	89	serious[a]	not serious	not serious	serious[c]	Sensitivity= 0.75 (0.62, 0.86)	LOW
		serious[a]	not serious	not serious	serious[c]	Specificity= 0.89 (0.74, 0.97)	LOW
Echogenic foci [joints only]							
1 study	131 joints	serious[a]	not serious	not serious	serious[c]	Sensitivity= 0.79 (0.68, 0.88)	LOW
		serious[a]	not serious	not serious	not serious	Specificity= 0.65 (0.52, 0.77)	MODERATE
Echogenic foci + DC sign [joints only]							
1 study	131 joints	serious[a]	not serious	not serious	serious[c]	Sensitivity= 0.34 (0.23, 0.46)	MODERATE
		serious[a]	not serious	not serious	not serious	Specificity=0.97 (0.88, 1.00)	MODERATE
Echogenic foci +/ or DC sign [joints only]							

Studies	No of Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 study	131 joints	serious[a]	not serious	not serious	serious[c]	Sensitivity= 0.86 (0.76, 0.93)	LOW
		serious[a]	not serious	not serious	not serious	Specificity=0.65 (0.52, 0.77)	MODERATE
DC sign + doppler activity [joints only]							
1 study	216	very serious[a]	not serious	not serious	not serious	Sensitivity= 0.68 (0.56, 0.78)	LOW
		very serious[a]	not serious	not serious	serious[c]	Specificity= 0.75 (0.67, 0.82)	VERY LOW
DC sign + doppler activity +SUA [joints only]							
1 study	216	very serious[a]	not serious	not serious	serious[c]	Sensitivity= 0.42 (0.31, 0.54)	VERY LOW
		very serious[a]	not serious	not serious	not serious	Specificity= 0.93 (0.87, 0.97)	LOW
DC sign [joints only]							
2 studies	347	very serious[a]	serious[b]	not serious	serious[c]	Sensitivity= 0.42 (0.31, 0.55)	VERY LOW
		very serious[a]	serious[b]	not serious	serious[c]	Specificity= 0.97 (0.88, 1.00)	VERY LOW
Tophi [joints only]							
1 study	131	serious[a]	not serious	not serious	not serious	Sensitivity= 0.28 (0.18, 0.40)	MODERATE
		serious[a]	not serious	not serious	not serious	Specificity= 1.00 (0.94, 1.00)	MODERATE
Erosions [joints only]							
1 study	131	serious[a]	not serious	not serious	serious[c]	Sensitivity= 0.39 (0.28, 0.52)	LOW
		serious[a]	not serious	not serious	serious[c]	Specificity= 0.62 (0.48, 0.74)	LOW

Studies	No of Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Diagnosis of gout [joints only]							
1 study	131	serious[a]	not serious	not serious	serious[c]	Sensitivity= 0.86 (0.76, 0.93)	LOW
		serious[a]	not serious	not serious	serious[c]	Specificity= 0.87 (0.75, 0.94)	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.

B Inconsistency was assessed by inspection of the sensitivity and specificity forest plots, using the point estimates and confidence intervals. Particular attention was paid to values above or below 50% (diagnosis based on chance alone) and the 80% threshold set by the GC (the threshold above which would be acceptable to recommend a test). The evidence was downgraded by 1 increment if the individual studies varied across 2 areas (for example 50-80% and 80-100%) and by 2 increments if the individual studies varied across 3 areas.

c 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).Where there were 3 studies, imprecision was assessed on confidence intervals produced by WinBUGS; where there were 2 studies the results from the study with the lowest sensitivity was used.

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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 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 4: Cost of diagnostic tests

Resource	Unit costs
Cost of blood test (excluding time to take blood)[a]	£3 – £4
Ultrasound scan with duration of less than 20 minutes (without contrast)	£63
Ultrasound scan with duration of less than 20 minutes (with contrast)	£52
Cost of X-Ray	£34
DECT	No unit costs available
Joint aspiration, 19 years and over	
Total HRG	£598
Elective (FCEs[b] = 524)	£1,439
Non-elective long-stay (FCEs[b] = 488)	£1,477
Non-elective short-stay (FCEs[b] = 5,509)	£715
Day case (FCEs[b] = 6,907)	£846
Regular day or night admissions (FCEs[b] = 17)	£208
Outpatient procedures (FCEs[b] = 8,061)	£219

Source: NHS Reference costs 2019/20[57]

(a) Directly accessed pathology services, haematology and phlebotomy respectively

(b) FCEs; Finished consultant episodes

Table 5: Cost of staff time

Resource	Unit costs
Primary care Practice Nurse (Band 5), cost per hour[a]	£42
General Practitioner, cost per consultation (9.22 minutes)[a]	£37

Source: PSSRU 2020[5]

(a) Including qualification costs but excluding individual and productivity costs.

1.1.10 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee considered sensitivity and specificity would be the best outcomes for judging the diagnostic accuracy of the different diagnostic approaches. The committee set clinical decision thresholds as sensitivity/specificity of 0.8, above which a test would be recommended. This is because a high level of sensitivity is important to avoid people with gout being missed and not getting access to treatment. A high level of specificity is important to avoid people without gout being misdiagnosed as having it and being treated unnecessarily. This could lead to people without gout taking medications, with their associated harms, for a substantial period of time. Sensitivity/specificity of 0.5 was identified as the point below which a test is of no clinical use, as the results could be due to chance.

1.1.11.2 The quality of the evidence

Only one small (n=55) study was included assessing the diagnostic accuracy of radiography, this was graded low. Three studies assessed the diagnostic accuracy of Dual energy CT (DECT), and although meta-analysed there were few participants (n=134) included. There was also inconsistency and imprecision, with an overall very low-quality grading so there was low confidence in the results. Most of the studies (n=7) included in the review assessed the accuracy of ultrasonography. A variety of signs associated with gout that could be identified by the ultrasonography were reported across the studies. These signs included DC sign, tophi, aggregates, erosions, synovial hypertrophy, doppler activity, echogenic foci, snowstorm and combinations of these. The number of signs meant the evidence was disparate. The committee thought that any of these features can be seen on ultrasound when looking for gout, however not all these features will be seen in each patient, and it is more likely to be a combination of some of them. The committee felt that studies should have looked at all of the established features for diagnosing gout on ultrasound, but most did not. The quality of the evidence assessing ultrasound varied from very low to high.

There were no studies available for clinical assessment or serum urate levels, or both combined for diagnosing gout.

1.1.11.3 Benefits and harms

There was no evidence for clinical assessment of the person with suspected gout, or for serum urate level testing or both combined. The committee considered the combination of clinical assessment and serum urate testing to be the most commonly used means of diagnosing gout, as most people with gout present to and are diagnosed in primary care.

Even though there was no evidence for the diagnostic accuracy of these, the committee agreed in their experience a combination of clinical assessment and serum urate testing is an effective and accessible method of diagnosing gout, providing that practitioners have the knowledge of the signs and symptoms to look out for. See evidence review B for further information on signs and symptoms. The committee agreed if a person presents with typical features of gout, such as rapid onset of severe pain, redness and swelling in the big toe or tophi, it would normally be unnecessary to carry out further tests other than measuring serum urate which should always be carried out to confirm hyperuricaemia. Therefore, the committee decided to recommend clinical assessment and serum urate testing initially when

gout is suspected. As this is usual, good practice a research recommendation was not thought necessary.

Joint aspiration of synovial fluid analysis is considered to be the gold standard for diagnosing gout and is typically carried out when there is diagnostic uncertainty after clinical assessment and serum urate level measurement. A definitive diagnosis of gout can be made if urate crystals are observed in the synovial fluid or tophi, but this procedure is not generally indicated unless a diagnosis of gout is in doubt or infection is suspected. Joint aspiration is not a simple option and is rarely conducted in primary care because practitioners may not have the necessary expertise to carry out the procedure, and also because the samples need to be analysed quickly and protected from light to prevent deterioration. Joint aspiration of synovial fluid is therefore usually carried out in secondary care. In addition, the committee noted any decision to undertake this procedure is dependent on the joint affected, because if the affected joint is small, it may not be possible to aspirate.

Where there is uncertainty in the diagnosis after clinical assessment and urate testing, joint aspiration of synovial fluid should be undertaken to confirm or refute the diagnosis and the committee made a recommendation to reflect this. However, the committee agreed that if this was not possible, such as where the joint is too small to aspirate, then imaging modalities could be considered. There was very high specificity (1.0) for radiography (plain X-ray), with no misdiagnosis of gout when compared to those identified by joint aspiration of synovial fluid. However, the sensitivity was low which means that many existing cases did not have radiographic features of gout and were missed. The committee acknowledged radiography is often the first choice to diagnose gout because it is easily accessible, and quick to undertake saving time in obtaining a result. However, because the sensitivity is poor this could lead to inefficiencies if a negative result would require further investigation. If radiography (plain x-ray) results are negative ultrasound is commonly used to confirm the diagnosis.

Dual energy CT (DECT) was found to be highly sensitive (0.95), and the specificity almost reached the 0.80 threshold (0.78), therefore the committee agreed this appeared a good alternative when joint aspiration of synovial fluid was not possible. However, the committee noted the quality of the evidence was very low and included only three small studies. The committee commented that there is very limited access to DECT in current practice. It is only available in secondary care and even then, access is limited due to lack of availability.

The studies assessing ultrasound reported a variety of signs associated with gout. These signs had varying sensitivity and specificity. As there were so many different signs with a range of quality the committee found this evidence difficult to interpret for the overall benefit of ultrasound in diagnosing gout. However, the committee agreed that in their experience ultrasound is useful in some settings, especially where DECT is not available. Ultrasound is more sensitive than plain X-ray. It has better diagnostic ability to confirm or refute the diagnosis. Similarly, to DECT access to joint ultrasound is limited, and typically only available in specialist MSK radiology services.

There was not an overwhelming confidence in the results or convincing case for one imaging modality over another, and in the committee's experience some may be more available depending on the healthcare/hospital settings, therefore they agreed to recommend all as options for the diagnosis of gout.

1.1.11.4 Cost effectiveness and resource use

No economic evaluations were identified for this review question. Unit costs were presented to aid consideration of cost effectiveness.

The committee discussed the clinical evidence and unit costs presented noting no clinical evidence was identified for diagnosing gout through history and examination assessment and serum urate level testing. The committee noted than in clinical practice gout is commonly diagnosed in primary care. However, if after assessment the diagnosis remains uncertain,

the person in question will be referred to rheumatology services. The committee noted that in current practice 1% - 5% of people with gout are referred to rheumatology with around 50% of these people being referred due to diagnostic uncertainty. The committee estimated that approximately two-thirds of people that are referred to rheumatology because of diagnostic uncertainty will have obtained a partial diagnosis of gout prior to referral.

Gout is typically diagnosed in general practice by taking a detailed history and physical examination and taking a serum urate level test (blood test) to measure serum urate concentrations. When there is diagnostic uncertainty joint aspiration can be undertaken. However, joint aspiration is rarely conducted in primary care because the aspirated samples need to be tested quickly and protected from light to ensure effective sample testing. In addition, in current practice, most GP practices only have samples collected once daily. Therefore, people with suspected gout need to have their joint aspirated close to the time of collections to ensure effective sample testing. Effective collection of primary care aspirated samples is also more challenging in rural settings because of the duration of time it takes for samples to reach testing facilities.

Joint aspiration is therefore more commonly performed in specialist musculoskeletal settings when the diagnosis of gout remains uncertain. The committee noted that joint aspiration is the most effective test to diagnose gout when there is diagnostic uncertainty. Therefore, upon referral to specialist settings, joint aspiration should be conducted if the affected joint is of sufficient size.

In instances where joint aspiration cannot be conducted (for example, because the affected joint is too small), or the diagnosis of gout remains uncertain, diagnostic imaging can be used to diagnose gout. X-ray can be used to detect any long-term damage in the affected joint(s) and rule out other diagnoses. The committee noted that DECT has good sensitivity and specificity to confirm or exclude a diagnosis of gout, but its availability is limited in current UK clinical practice. Ultrasound is more likely to be available, if required, to aid in the diagnosis of gout.

The recommendations made by the committee are reflective of current practice and therefore are not expected to result in a substantial resource impact.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.6 to 1.1.8.

1.1.13 References

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Appendices

Appendix A – Review protocols

Review protocol for approaches for diagnosing gout

ID	Field	Content
0.	PROSPERO registration number	Not applicable
1.	Review title	The most accurate and cost-effective approaches to diagnosing gout, in particular serum urate level compared with joint aspiration?
2.	Review question	2.2 What are the most accurate and cost-effective approaches to diagnosing gout, in particular serum urate level compared with joint aspiration?
3.	Objective	To determine which approaches for diagnosing gout are the most accurate and cost-effective.
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

		Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout.
7.	Index test/approach	• Clinical assessment (history and examination) • Serum urate level (persistently above 380 micromol/L) • Clinical assessment plus serum urate level (history and examination plus serum urate level persistently above 380 micromol/L) • X-ray • Ultrasound • Dual-energy CT (DECT)
8.	Reference standard	• Joint aspiration (urate crystals are observed in synovial fluid or tophi)
9.	Types of study to be included	Diagnostic accuracy cross-sectional studies. Systematic reviews of diagnostic accuracy cross-sectional studies.
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	The 'gold standard' for diagnosing gout is looking for urate crystals in synovial fluid, however testing for urate crystals is not always possible therefore other means of diagnosis would be useful for practical reasons.
12.	Primary outcomes (critical outcomes)	Primary paired outcome: Sensitivity/specificity
13.	Secondary outcomes (important outcomes)	N/A
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 manual section 6.4). 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	The Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklist will be used (see Appendix H in the NICE guidelines manual 2014[54]).
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.
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Setting
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	21st May 2021
22.	Anticipated completion date	13th June 2022

<table>
<tr><td>23.</td><td>Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td></td><td></td><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td></td><td></td><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td></td><td></td><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☑</td></tr>
<tr><td></td><td></td><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td></td><td></td><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td></td><td></td><td>Data analysis</td><td>☐</td><td>☐</td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">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</td></tr>
<tr><td>25.</td><td>Review team members</td><td colspan="3">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]</td></tr>
<tr><td>26.</td><td>Funding sources/sponsor</td><td colspan="3">This systematic review is being completed by the National Guideline Centre which receives funding from NICE.</td></tr>
<tr><td>27.</td><td>Conflicts of interest</td><td colspan="3">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</td></tr>
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		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).[54] **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 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.[54]

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 6: 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 7: 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.

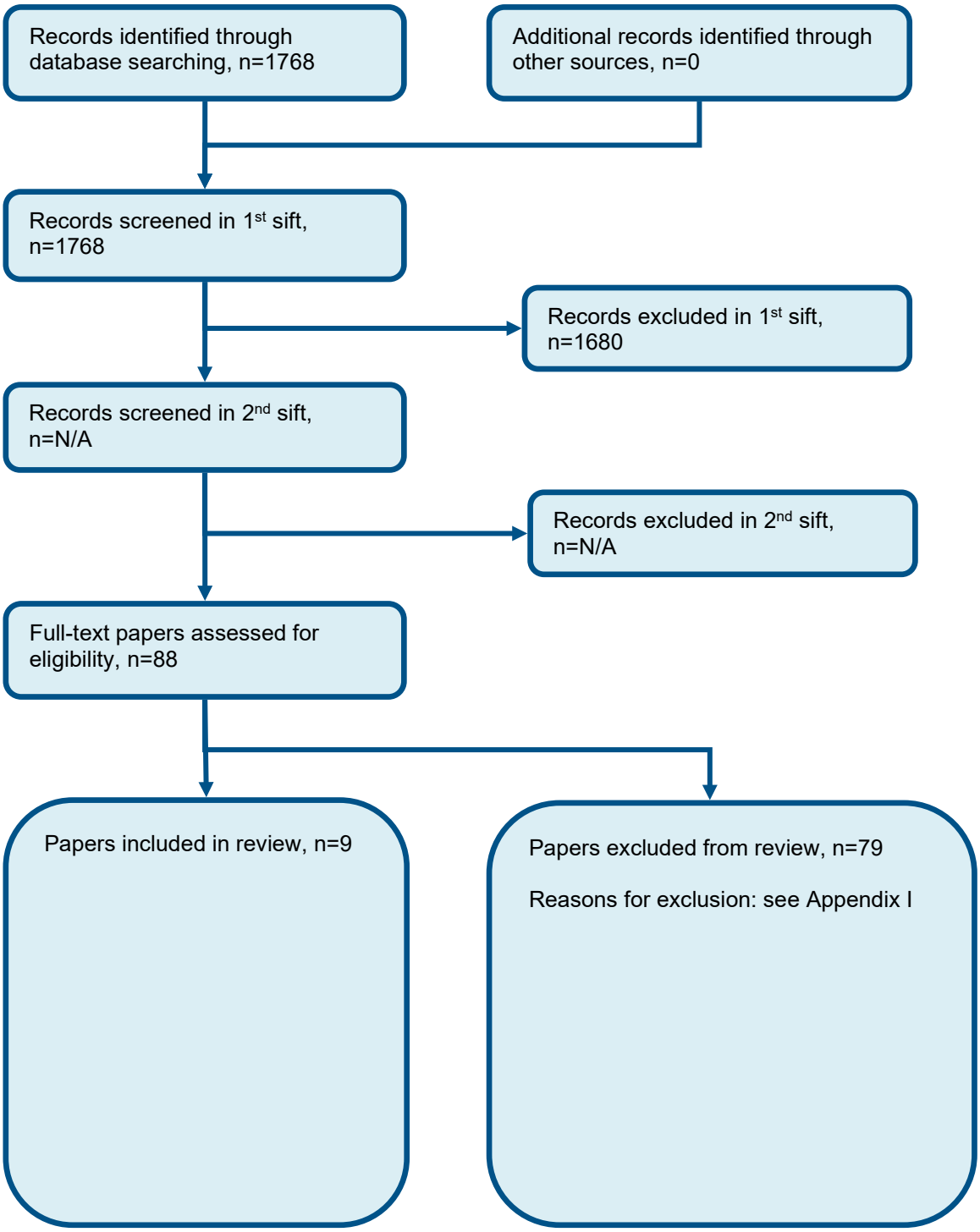
58.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
59.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
60.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
61.	(sf12* or sf 12* or short form 12* or shortform 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 approaches for diagnosis of gout



Appendix D –Diagnostic evidence

Reference	**Ahmad 2016**[1Ahmad2016]
Study type	Diagnostic accuracy study
Study methodology	Data source: not stated Recruitment: not reported
Number of patients	n = 90 (all patients underwent radiography and DECT of bilateral feet and knees: 360 joints. Each foot, including the ankle, was taken as a single joint).
Patient characteristics	Age, median (range): 44years (21-75 years) Gender (male to female ratio):87M/ 3F Ethnicity: not reported Setting: not reported 66/90 were in the acute stage of arthritis, 11/90 were in the inter-critical stage, 13/90 were in the chronic stage Average duration of gout/ arthritis was 6.1 years Country: India Inclusion criteria: clinically suspected gout, based on history (especially with respect to American College of Rheumatology clinic-radiologic criteria) and serum uric acid levels. Exclusion criteria: not reported
Target condition(s)	Gout
Index test(s) and reference standard	Index test: digital plain radiography Digital plain radiographs of bilateral feet and knees were taken in two orthogonal planes on a flat panel detector system. Radiographs were assessed for morphological characteristics, such as periarticular punched out erosions, soft tissue/ intra-articular tophi and/ or soft tissue swelling. A characteristic finding in any of the examined joint sites was enough to label the patient as having gout. Index test: dual-energy computed tomography

Reference	**Ahmad 2016**[1Ahmad2016]				
	Radiographs and non-contrast CT scans that had already been assessed for morphological characteristics of gout, were read with dual energy software (Syngo Dual Energy). For the detection and localization of urate deposits, the weighted average images provided by the image reconstruction system were evaluated. Joints were screened in all three planes along with volume-rendered images. Each joint was classified as positive or negative for the presence of uric acid crystals. Positive findings in a single joint was enough to label the patient as having gout. Reference standard: joint aspiration The most severely affected joint was aspirated within a week of DECT and the fluid was examined under polarizing microscope for the presence of negatively bifringent uric acid crystals. Results of joint aspiration were considered positive when aspiration demonstrated uric acid crystals at polarized microscopic examination. Results were considered negative when no uric acid crystals were visualized. In these patients, serum uric acid levels were also recorded so that they could be associated with dual-energy CT. Time between measurement of index test and reference standard: within a week				
2×2 table radiography		Reference standard +	Reference standard −	Total	
	Index test +	8	0	8	
	Index test −	22	25	47	
	Total	30	25	55	
2×2 table DECT		Reference standard +	Reference standard −	Total	
	Index test +	30	13	43	
	Index test −	0	12	12	
	Total	30	25	55	
Statistical measures	<u>Index test: radiographs</u> Sensitivity for aspiration positive estimate: 27% 8/30 (95%CI: 13%, 46%) Specificity for aspiration negative estimate: 100% 25/25 (95%CI: 83%, 100%) <u>Index test: DECT</u> Sensitivity for aspiration positive estimate: 100% 30/30 (95%CI: 86%, 100%) Specificity for aspiration negative estimate: 48% 12/25 (95%CI: 28%, 68%)				
Source of funding	Not reported				

Reference	**Ahmad 2016**[1Ahmad2016]
Limitations	Risk of bias: very high-selection bias, interpretation bias ,flow and timing [recruitment of patients unclear, did not state qualifications of those who interpreted the index test, index test was interpreted not blinded to clinical and other radiological findings, unclear if ref std interpreted blind, not all patients received the reference standard] Indirectness: none
Comments	Year: April 2011- March 2013 35 patients did not receive the reference standard due to an acutely painful joint. Also reports sensitivity and specificity of radiography and DECT with joint aspiration plus ACR criteria as reference standard.

Reference	**Christiansen 2021**[17Christiansen2021]
Study type	Cross-sectional
Study methodology	Data source: not reported Recruitment: consecutive
Number of patients	n = 82
Patient characteristics	Age, mean (range): 62.4 years (19-88 years) Gender (male to female ratio):70M/ 12F Ethnicity: not reported Setting: Centre for Rheumatology and Spine Diseases Country: Denmark Inclusion criteria: Adults (≥18 years) referred from primary care or other hospital departments with clinical suspicion of gout. Exclusion criteria: Recent (<6 weeks) glucocorticoid injection or oral glucocorticoid.
Target condition(s)	Gout
Index test(s) and reference standard	Index test: ultrasound scan Performed using a GE LogiqE9 machine (GE Healthcare, Milwaukee, WI, USA) by one sonographer before joint/ tophus puncture and blinded to microscopy findings. All patients had ultrasound performed bilaterally of joints [MCP 1-5, wrist, elbow, MTP 1-5, tibiotalar, knee], tendons [extensors of the wrist (scored as individual compartments 1-6), peroneus (longus and brevis scored as one) and tibialis posterior], and tendon insertions [triceps, quadriceps, proximal and distal patellar ligament, and Achilles], In all regions, the four gout

Reference	Christiansen 2021[17Christiansen2021]				
	lesions were scored separately. Additionally, concomitant synovial hypertrophy was graded semi-quantitively by grey scale and hyperaemia by colour Doppler according to the OMERACT scoring system. The sums of all individual gout lesions across all scanned sites were calculated for each patient. Reference standard Puncture of a joint/ tophus was attempted in all patients in a currently/ previously inflamed joint/ tophus, either as an aspiration of fluid or as a dry needle aspiration. The sample was examined by independent assessors (both certified examiners) blinded to ultrasound findings. If no MSU crystals were identified the puncture was repeated after 2 weeks. All samples were evaluated using an Olympus microscope. Time between measurement of index test and reference standard: within a week				
2×2 table DC sign		Reference standard +	Reference standard −	Total	
	Index test +	46	3	49	
	Index test −	11	22	33	
	Total	57	25	82	
2×2 table tophi		Reference standard +	Reference standard −	Total	
	Index test +	45	2	47	
	Index test −	12	23	35	
	Total	57	25	82	
2×2 table aggregates		Reference standard +	Reference standard −	Total	
	Index test +	54	17	71	
	Index test −	3	8	11	
	Total	57	25	82	
2×2 table erosions		Reference standard +	Reference standard −	Total	
	Index test +	44	11	55	
	Index test −	13	14	27	
	Total	57	25	82	
2×2 table Synovial hypertrophy		Reference standard +	Reference standard −	Total	
	Index test +	56	23	79	
	Index test −	1	2	3	
	Total	57	25	82	

Reference	**Christiansen 2021**[17Christiansen2021]				
2×2 table Doppler activity		Reference standard +	Reference standard −	Total	
	Index test +	46	14	60	
	Index test −	11	11	22	
	Total	57	25	82	
Statistical measures	Index text: ultrasound scan: double contour sign Sensitivity: 81% (95%CI: 68%, 90%) 46/57 Specificity: 88% (95%CI: 69%, 97%) 22/25 Index text: ultrasound scan: tophi Sensitivity: 79% (95%CI: 66%, 90%) 45/57 Specificity: 92% (95%CI: 74%, 99%) 23/25 Index text: ultrasound scan: aggregates Sensitivity: 95% (95%CI: 85%, 9%) 54/57 Specificity: 32% (95%CI: 15%, 54%) 8/25 Index text: ultrasound scan: erosions Sensitivity: 77% (95%CI: 64%, 87%) 44/57 Specificity: 56% (95%CI: 35%, 76%) 14/25 Index text: ultrasound scan: synovial hypertrophy Sensitivity: 98% (95%CI: 91%, 100%) 56/57 Specificity: 8% (95%CI: 1%, 26%) 2/25 Index text: ultrasound scan: doppler activity Sensitivity: 81% (95%CI: 68%, 90%) 46/57 Specificity: 44% (95%CI: 24%, 65%) 11/25				
Source of funding	Supported by research grants from the Danish Rheumatism Association				
Limitations	Risk of bias: none				

Reference	**Christiansen 2021**[17Christiansen2021]
	Indirectness: none
Comments	Uses OMERACT criteria for ultrasound scanning

Reference	**Elsaman 2016**[24Elsaman2016]
Study type	Cross-sectional
Study methodology	Data source: not stated Recruitment: not stated
Number of patients	n =100 (a total of 131 joints were examined: one knee in 55 participants, two knees in 12 participants, one first MTP joint in 14 participants, and one knee plus one first MTP joint in 19 participants, for a total of 98 knees and 33 first MTP joints examined).
Patient characteristics	Age, mean (range): 53.1years (40-75 years) Gender (male to female ratio):55M/ 45F Ethnicity: not reported Setting: ambulatory care Country: Egypt Inclusion criteria: undifferentiated arthritis either untreated or treated with only NSAIDs. Exclusion criteria: any known cause of arthritis, including rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, scleroderma, neuropathic arthritis, seronegative spondyloarthropathy, known gouty arthritis and similar conditions.
Target condition(s)	Gout
Index test(s) and reference standard	Index test: Ultrasound scan Performed in both the anterior longitudinal suprapatellar median and paramedian and transverse planes. Posterior longitudinal and transverse examinations were also done. The first MTP joint was examined from dorsal, lateral and plantar views in the longitudinal and transverse planes. Reference standard: joint aspiration Polarizing light microscopy was used. Slides were usually prepared in <48 hours.

Reference	Elsaman 2016[24Elsaman2016]				
	Time between measurement of index test and reference standard: within a week				
2×2 table US diagnosis of gout		Reference standard +	Reference standard −	Total	
	Index test +	61	8	69	
	Index test −	10	52	62	
	Total	71	60	131	
2×2 table Echogenic foci by US		Reference standard +	Reference standard −	Total	
	Index test +	56	21	77	
	Index test −	15	39	54	
	Total	71	60	131	
2×2 table Erosions by US		Reference standard +	Reference standard −	Total	
	Index test +	28	23	51	
	Index test −	43	37	80	
	Total	71	60	131	
2×2 table DC sign by US		Reference standard +	Reference standard −	Total	
	Index test +	30	2	32	
	Index test −	41	58	99	
	Total	71	60	131	
2×2 table tophi by US		Reference standard +	Reference standard −	Total	
	Index test +	20	0	20	
	Index test −	51	60	111	
	Total	71	60	131	
2×2 table Echogenic foci+ double contour		Reference standard +	Reference standard −	Total	
	Index test +	24	2	26	
	Index test −	47	58	105	
	Total	71	60	131	
2×2 table		Reference standard +	Reference standard −	Total	
	Index test +	61	21	82	
	Index test −	10	39	49	

Reference	**Elsaman 2016**[24Elsaman2016]				
Echogenic foci+/or double contour	Total	71	60	131	
Statistical measures	Index text: ultrasound scan detecting gouty arthritis Sensitivity for aspiration positive estimate: 85.9% Specificity for aspiration negative estimate: 86.7% Echogenic foci by US Sensitivity: 78.9% Specificity: 65.0% Erosions by US Sensitivity: 39.4% Specificity: 61.7% Double contour sign by US Sensitivity: 42.3% Specificity: 96.7% Tophi by US Sensitivity: 28.2% Specificity: 100.0% Echogenic foci + double contour Sensitivity: 33.8% Specificity: 96.7% Echogenic foci +/or double contour Sensitivity: 85.9% Specificity: 65.0%				
Source of funding	Supported by German-Egyptian Scientific Project Grant 51309219 from the German Academic Exchange Service and the Ministry of Higher Education and Scientific Research of the Arab Republic of Egypt.				

Reference	Elsaman 2016[24Elsaman2016]
Limitations	Risk of bias: very high: selection bias, interpretation bias, flow and timing [selection of patients unclear, unclear if reference standard was interpreted blinded to index test results. Unclear interval between index test and reference standard] Indirectness: none
Comments	Diagnosis based on total number of joints, not patients. All patients enrolled in the study had a BMI>23 Confidence intervals and prevalence not reported

Reference	Glazebrook 2011[31Glazebrook2011]
Study type	Retrospective cohort
Study methodology	Data source: not reported Recruitment: consecutive patients
Number of patients	n = 94 (144 dual-energy CT scans were obtained: 2 joints were examined in 21 patients, 3 joints were examined on two patients, and one patient underwent two examinations 8 months apart).
Patient characteristics	Age, mean (range): 62.7 years (29-89 years) Gender (male to female ratio):53M/ 41F Ethnicity: not reported Setting: not reported Country: USA Inclusion criteria: (a) signed consent from the patient to use past medical data for research purposes, (b) clinical suspicion of the presence of monosodium urate crystals in the examined joint by the rheumatologist or orthopaedic surgeon caring for the patient, (c) clinical ordering of dual-energy CT examination for clinical purposes to rule in or exclude euric acid crystals in the most affected joint or joints, and (d) dual-energy CT examination of the painful joint performed with the gout protocol between April 2008 and February 2010. Exclusion criteria: not reported
Target condition(s)	Gout
Index test(s) and reference standard	Index test: dual-energy computed tomography

<table>
<tr><td>Reference</td><td colspan="5">Glazebrook 2011[31Glazebrook2011]</td></tr>
<tr><td></td><td colspan="5">Images were evaluated by two musculoskeletal radiologists, blinded to patients' clinical data using a commercially available workstation (Dual-energy version, Syngo CT Workplace; Siemens Healthcare). Axial images, as well as images reconstructed in the sagittal and coronal planes were reviewed.
Examinations were classified as positive or negative for the presence of monosodium urate crystals. The presence of artifacts was graded according to a four point scale that takes into consideration the influence of any artifacts on the diagnostic confidence (grade 1, no artifacts, high confidence in diagnostic capability; grade 2, presence of artifacts, but no change in confidence; grade 3, presence of artifacts causing decreased confidence; grade 4, severe artifacts, nondiagnostic).
In patients in whom more than one joint was scanned, a positive finding in any single joint was sufficient to consider the patient to have gout.
The first 53 patients were examined with the first generation scanner, and the remaining 41 were examined with the second-generation scanner.

Reference standard: joint aspiration
Results of joint aspiration were considered positive when aspiration demonstrated uric acid crystals at polarized microscopic examination. Results were considered negative when no uric acid crystals were visualized. In these patients, serum uric acid levels were also recorded so that they could be associated with dual-energy CT.

Time between measurement of index test and reference standard: within a month</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td></td></tr>
<tr><td></td><td>Index test +</td><td>12</td><td>2</td><td>14</td><td></td></tr>
<tr><td></td><td>Index test −</td><td>0</td><td>17</td><td>17</td><td></td></tr>
<tr><td></td><td>Total</td><td>12</td><td>19</td><td>31</td><td></td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text: dualenergy computed tomography for the identification of uric acid crystals and a diagnosis of gout
Sensitivity for aspiration positive estimate, n=12: 100% (95%CI: 74%, 100%) for both readers
Specificity for aspiration negative estimate, n=19: 89% (95%CI: 67%, 99%) for reader 1, 79% (95%CI 54%, 94%) for reader 2, 89% for consensus (95%CI 67%, 99%).</td></tr>
<tr><td>Source of funding</td><td colspan="5">Not reported</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: very high [retrospective study, flow and timing, two different CT scanners were used for the index test. unclear if reference standard was interpreted blind]
Indirectness: population may not be representative as it included mainly atypical presentations of gout,</td></tr>
</table>

Reference	**Glazebrook 2011**[31Glazebrook2011]
Comments	Year 2008-2010 53 patients were excluded because they had enrolled in a different study.

Reference	**Lamers-Karnebeck, 2014**[44 Lamers-Karnebeck2014]
Study type	Diagnostic accuracy study
Study methodology	Data source: not stated Recruitment: sequential patients
Number of patients	n =54.
Patient characteristics	Age, mean (range): MSU proven gout group: 63.5 (55.5-69.5), Non MSU proven gout group: 55.0 (41.8-63.5) Gender (male to female ratio):MSU proven gout group: 25M/ 1F, Non MSU proven gout group: 13M/ 15F Ethnicity: not reported Setting: academic hospital Country: The Netherlands Inclusion criteria: acute mono/ oligoarthritis
Target condition(s)	Gout/ MSU arthritis
Index test(s) and reference standard	Index test: Ultrasound scan An USS was performed on 6 joints: the joint with arthritis, the contralateral side, and two other joints bilaterally. The ultrasonographers were two rheumatologists and two trainees. All the joints were viewed at least by two ultrasonographers separately at the time of patient presentation. Reference standard: joint aspiration Performed on the clinically affected joint Time between measurement of index test and reference standard: unclear

Reference	**Lamers-Karnebeck, 2014**[44 Lamers-Karnebeck2014]				
2×2 table Any US abnormality		Reference standard +	Reference standard −	Total	
	Index test +	25	9	34	
	Index test −	1	19	20	
	Total	26	28	54	
2×2 table DC sign		Reference standard +	Reference standard −	Total	
	Index test +	20	7	27	
	Index test −	6	21	27	
	Total	26	28	54	
2×2 table snowstorm		Reference standard +	Reference standard −	Total	
	Index test +	10	4	14	
	Index test −	16	24	40	
	Total	26	28	54	
2×2 table Tophus presence		Reference standard +	Reference standard −	Total	
	Index test +	5	2	7	
	Index test −	21	26	47	
	Total	26	28	54	
Statistical measures **N=26**	Index text: ultrasound scan: any abnormality Prevalence: in gout: 25/26 Prevalence in studied population: 34/54 Sensitivity: 96% (95% CI 95-97%) Specificity: 68% (95% CI 63-73%) Index text: ultrasound scan: double contour sign Prevalence: in gout: 20/26 Prevalence in studied population: 27/54 Sensitivity: 77% (95% CI 72-81%) Specificity: 75% (95% CI 66-84%) Index text: ultrasound scan: snow-storm appearance Prevalence: in gout: 10/26 Prevalence in studied population: 14/54 Sensitivity: 38% (95% CI 34-42%)				

Reference	**Lamers-Karnebeck, 2014**[44 Lamers-Karnebeck2014]
	Specificity: 86% (95% CI 83-89%) Index text: ultrasound scan: tophus presence Prevalence: in gout: 5/26 Prevalence in studied population: 7/54 Sensitivity: 19% (95% CI 17-22%) Specificity: 93% (95% CI 91-95%)
Source of funding	None stated
Limitations	Risk of bias: high for unclear reference standard blinding and unclear flow and timing Indirectness: none
Comments	Same observers for some index test and reference standard.

Reference	**Loffler, 2015**[50Loffler2015]
Study type	Diagnostic accuracy study
Study methodology	Data source: not stated Recruitment: retrospective
Number of patients	n =225 joints (number of patients not reported).
Patient characteristics	Age, mean (range): 64 (18-93) years Gender (male to female ratio): 1.7:1 Ethnicity: not reported Setting: rheumatology department Country: Germany Inclusion criteria: acute mono/ oligoarthritis. Every type and size of joint was included.
Target condition(s)	Gout

Reference	**Loffler, 2015**[50Loffler2015]				
Index test(s) and reference standard	Index test: Ultrasound scan All patients received an ultrasound of the affected joint, one by physician(blinded to the diagnosis) with at least 2 years experience in joint sonography. All sonographers were specially trained in joint sonography and certified by the standards of the German Society of Ultrasound in Medicine (DEGUM). Two of them were DEHUM level 2 and 3 sonographers (3 being the highest DEGUM certification, i.e., US trained). Two devices were used (Aplio 400, Toshiba), and a Xario XG, Toshiba. Cartilage enhancements presenting as a line parallel to the bony articular surface were characterised as DC sign. A total of 6 physicians performed the US, but the level of experience varied. In difficult cases, a less experienced examiner consulted a more experienced colleague to verify findings. This was not standardised. Findings were not routinely confirmed by a second sonographer blinded to the first results. Reference standard: joint aspiration All patients underwent SF analysis by needle aspiration of the affected joint. SFspecimens were analysed by a consultant in pathology using polarizing microscopy. The presence of phagocytized MSU crystals was diagnostic for gout. Time between measurement of index test and reference standard: unclear				
2×2 table DC sign		Reference standard +	Reference standard −	Total	
	Index test +	65	51	116	
	Index test −	9	91	100	
	Total	74	142	216	
2×2 table DC sign/ Doppler with hypervascularisation		Reference standard +	Reference standard −	Total	
	Index test +	50	35	85	
	Index test −	24	107	131	
	Total	74	142	216	
2×2 table DC sign/ Doppler with hypervascularisation + serum uric acid		Reference standard +	Reference standard −	Total	
	Index test +	31	10	41	
	Index test −	43	132	175	
	Total	74	142	216	

Reference	**Loffler, 2015**[50Loffler2015]
Statistical measures	Index text: ultrasound scan: DC sign Sensitivity: 87.8% Specificity: 64.1% Index text: ultrasound scan: DC sign/ Doppler with hypervascularization Sensitivity: 67.6% Specificity: 75.4% Index text: ultrasound scan: DC sign/ Doppler with hypervascularization+ serum uric acid Sensitivity: 42.0% Specificity: 92.3%
Source of funding	Funding not stated
Limitations	None stated Risk of bias: high for unclear reference standard blinding and unclear flow and timing Indirectness: none
Comments	9 cases (4%) had both gout and CPPD as identified by MSU and CPP crystals in the same SF specimen. These were excluded from the analysis.

Reference	**Ogdie 2017**[61Ogdie2017]
Study type	Cross-sectional
Study methodology	Data source: data from the Study for Updated Gout Classification Criteria (SUGAR) Recruitment: SUGAR study recruited consecutive patients.
Number of patients	n =824

Reference	Ogdie 2017[61Ogdie2017]
Patient characteristics	Age, mean (SD): 60.2 years (14.6 years) for cases, 59.5 years (16.0 years) for controls Gender (male):87% for cases, 54% for controls Ethnicity: cases: White/ European/ Caucasian:65%, African/ Black 1%, Hispanic 5%, South Asian 10%, East Asian 16%, Pacific Island 0.7%, Other indigenous 0.7%, Other 1% controls: White/ European/ Caucasian:54%, African/ Black 2%, Hispanic 5%, South Asian 9%, East Asian 27%, Pacific Island 0.3%, Other indigenous 1%, Other 2% Number of episodes Cases: 1:9 %, 2-5: 22%, >5: 69% Controls: 1: 23%, 2-5: 28%, >5: 49% Previous diagnosis of gout Cases: 83% Controls: 28% Current urate lowering therapy Cases: 35% Controls: 9% Suspected clinical tophus Cases: 36% Controls: 5% Setting: rheumatology clinics Country: multiple countries Inclusion criteria: ≥1 swollen joint or a subcutaneous nodule; differential diagnosis of gout.
Target condition(s)	Gout

Reference	**Ogdie 2017**[61Ogdie2017]				
Index test(s) and reference standard	Index test: ultrasound scan US was performed for a single joint in most patients; however it was performed for more than 1 joint in 16% of the patients. The most commonly examined joints were the knees, MTP joints and ankles. US was performed on 1 or more clinically affected joints by either rheumatologists or radiologists who were blinded with regard to the aspiration results. All ultrasonographers had prior US training. US double contour sign was defined as hyperechoic band on the surface of the articular cartilage. US tophus was defined as the presence of a hyperechoic, heterogeneous lesion surrounded by an anechoic rim. US snowstorm was defined as a 'snowstorm type joint effusion'. These definitions were provided in the clinical research form. A variety of machines were used and many different ultrasonographers performed the US. Ultrasonographers were mainly rheumatologists who used US in clinical practice, although they were not necessarily certified, or radiologists. Although definitions of US features were provided to all ultrasonographers, a standardised scanning protocol was not required. Reference standard: crystal based diagnosis following arthrocentesis or soft tissue nodule aspiration Crystal identification was performed by trained observers who were required to pass a certification procedure, which included a web-based crystal recognition test and the examination of 5 vials of synovial fluid.Only sites with participants who completed this certification were able to participate in the study. Cases were subjects with confirmed MSU crystals, and controls were subjects with a joint fluid or soft tissue nodule aspirate that was negative for MSU crystals. Time between measurement of index test and reference standard: not stated				
2×2 table Any US feature		Reference standard +	Reference standard −	Total	
	Index test +	320	64	384	
	Index test −	96	344	440	
	Total	416	408	824	
2×2 table DC sign		Reference standard +	Reference standard −	Total	
	Index test +	249	35	284	
	Index test −	165	373	538	
	Total	414	408	822	
2×2 table tophus		Reference standard +	Reference standard −	Total	
	Index test +	189	21	576	
	Index test −	222	387	243	
	Total	411	408	819	
2×2 table snowstorm		Reference standard +	Reference standard −	Total	
	Index test +	125	37	162	

Reference	**Ogdie 2017**[61Ogdie2017]				
	Index test −	287	370	657	
	Total	412	407	819	
Statistical measures	Index text: ultrasound scan: any US feature Sensitivity for any US feature: 76.9% (95% CI:72.6-80.9%) Specificity for any US feature: 84.3% (95% CI:80.4-87.7%) Index text: ultrasound scan: 2 US features Sensitivity: 44.0% (95% CI:39.2-48.9%) Specificity: 95.3% (95% CI:92.8-97.2%) Index text: ultrasound scan: 3 US features Sensitivity: 14.4% (95% CI:11.2-18.2%) Specificity: 97.6% (95% CI:95.6-98.8%) Index text: ultrasound scan: double contour sign Sensitivity: 60.1% (95% CI:55.2-64.9%) Specificity: 91.4% (95% CI:88.3-94.0%) Index text: ultrasound scan: tophus Sensitivity: 46.0% (95% CI:41.1-50.9%) Specificity: 94.9% (95% CI:92.2-96.8%) Index text: ultrasound scan: snowstorm Sensitivity: 30.3% (95% CI:25.9-35.0%) Specificity: 90.9% (95% CI:87.7-93.5%)				
Source of funding	Supported by the American College of Rheumatology (Classification Criteria grant), the European League Against Rheumatism Classification Criteria grant),, Arthritis New Zealand, Association Rheumatisme et Travail, and Asociacion de Reumatologos del Hospital de Cruces.				
Limitations	Risk of bias: very high [patient selection bias as not all had the index test, index test had variations in US machine use, and interpretation bias due to variations in training and lack of a threshold. Timing between tests was not described, reference standard was obtained by 2 methods.]				

Reference	**Ogdie 2017**[61Ogdie2017]
	Indirectness: none
Comments	Not all patients received ultrasound scanning due to the availability ultrasound and of trained ultrasonographers at enrolling sites.

Reference	**Pattamapaspong, 2017**[65Pattamapaspong2017]
Study type	Retrospective cohort
Study methodology	Data source: patients enrolled in two prospective studies designed to update the gout classification criteria, and to assess the performance of the existing criteria (SUGAR study) Recruitment: consecutive patients
Number of patients	n = 100 (89 of these were included in this retrospective analysis who had undergone joint aspiration and ultrasound scanning of the same symptomatic joint 18 to 36 months earlier)
Patient characteristics	Age, mean (range): 65 years (18-87 years) Gender (male to female ratio): 60M/29F Ethnicity: not reported Setting: inpatients Country:Thailand Inclusion criteria: acute arthritis, as diagnosed by a rheumatologist who confirmed the presence of painful swelling of at least one joint within 14 days of symptom onset.
Target condition(s)	Gout
Index test(s) and reference standard	Index test: Ultrasound scan All US studies were performed by a musculoskeletal radiologist with 15 years of experience who was blinded to the diagnosis and used a single machine for all patients (Aplio500, Toshiba Medical System, Tochigi, Japan). Before interpreting the images, three of the co-authors together viewed US images of joints from various sources, to clarify the definitions of US features of gout. The definitions reported in the OMERACT and others (Fodor, Girish, Ottaviani) were used. The scans were interpreted by a musculoskeletal fellow in training with 3 years of experience in joint US and a board certified radiologist with 2 years of experience (blind readers). All recorded images were then interpreted independently to determine the presence or absence of feature es of gout by both blinded readers.

Reference	Pattamapaspong, 2017[65Pattamapaspong2017]				
	Reference standard: joint aspiration Joint aspiration and an immediate microscopic examination. Time between measurement of index test and reference standard: 2.7/ 3.6 days mean (range 0-7). 84 patients underwent joint aspiration, followed by US with a mean delay of 2.7 days after US (range 0-7 days). The remaining 5 patients had the US first, followed by joint aspiration with a mean delay of 3.6 days after US (range 0-7 days).				
2×2 table DC sign		Reference standard +	Reference standard −	Total	
	Index test +	22	3	25	
	Index test −	31	33	64	
	Total	53	36	89	
2×2 table Intra-articular aggregates		Reference standard +	Reference standard −	Total	
	Index test +	31	3	34	
	Index test −	22	33	55	
	Total	53	36	89	
2x2 table tophi		Reference standard +	Reference standard −	Total	
	Index test +	21	0	21	
	Index test −	32	36	68	
	Total	53	36	89	
2x2 table Any of the 3 features		Reference standard +	Reference standard −	Total	
	Index test +	40	4	44	
	Index test −	13	32	45	
	Total	53	36	89	
2x2 table All 3 features		Reference standard +	Reference standard −	Total	
	Index test +	9	0	9	
	Index test −	44	36	80	
	Total	53	36	89	

Reference	**Pattamapaspong, 2017**[65Pattamapaspong2017]
Statistical measures	Index text: ultrasound scan: double contour sign Sensitivity: 42% 22/53 Specificity: 92% 33/36 Index text: ultrasound scan: intra-articular aggregates Sensitivity: 58% 31/53 Specificity: 92% 33/36 Index text: ultrasound scan: tophi Sensitivity: 40% 21/53 Specificity: 100% 36/36 Index text: ultrasound scan: any of the 3 features Sensitivity: 75% 40/53 Specificity: 89% 32/36 Index text: ultrasound scan: all 3 features Sensitivity: 17% 9/53 Specificity: 100% 36/36
Source of funding	Stated to be none
Limitations	Risk of bias: serious [flow and timing, reference standard protocol not described] Indirectness: included patients already diagnosed with gout/ hospitalised patients
Comments	Year January 2013-2 June 2014 Inpatient population Retrospective study of patients with previous joint aspiration. Only the most inflamed joint was scanned, even if there were multiple affected joints- may not be representative of MTP joint which is the most commonly affected. .

Reference	**Singh 2021**[75Singh2021]
Study type	Cross-sectional
Study methodology	Data source: patients from a single outpatient rheumatology clinic at a tertiary care hospital in the CRYSTALILLE inception cohort. Recruitment: not stated
Number of patients	n = 147 (48 had joint fluid aspiration and were included in the analysis)
Patient characteristics	Age, mean (SD): 64.7 years (14.4 years) Gender (male to female ratio): 127M/ 20F Ethnicity: not reported Setting: outpatient rheumatology clinic at a tertiary-care hospital Country: France Inclusion criteria: newly referred to the clinic for establishing a diagnosis of gout (n=92), assisting with gout management (n=55)
Target condition(s)	Gout
Index test(s) and reference standard	Index test: DECT Performed using a single-source CT system (Somatom Definition Edge; Siemens Healthineers). Ankles/feet and knees were scanned in two consecutive acquisitions with a standardised CT data acquisition and image reconstruction protocol. Analysed by one musculoskeletal radiologist who was blinded to patients' clinical features. A positive DECT scan was defined as the presence of typical colour-coded MSU crystal deposits at articular or periarticular sites from a minimum threshold volume of 0.01cm3. Index test: ultrasound scan Performed within a week of DECT by 1 of 4 trained musculoskeletal radiologists (with 18,7 , 7 and 6 years of experience) blinded to clinical features. The two most reliable ultrasound elementary lesions in gout- DC sign and tophus were assessed as per the OMERACT Ultrasound Gout Task Force definitions. The DC sign was evaluated at the patellofemoral, tibiotalar and 1st metatarsophalangeal joints bilaterally. Tophi were searched for at both feet/ ankles and knees.

Reference	**Singh 2021**[75Singh2021]				
	Reference standard: joint aspiration Patients were classified as gout based on the presence of MSU crystals in the SFA by polarized light microscopy. Time between measurement of index test and reference standard: not stated				
2×2 table ultrasound		Reference standard +	Reference standard −	Total	
	Index test +	32	4	36	
	Index test −	6	6	12	
	Total	38	10	48	
2×2 table Ultrasound: DC sign		Reference standard +	Reference standard −	Total	
	Index test +	31	4	35	
	Index test −	7	6	13	
	Total	38	10	48	
2×2 table Ultrasound: tophus		Reference standard +	Reference standard −	Total	
	Index test +	23	2	25	
	Index test −	15	8	23	
	Total	38	10	48	
2×2 table DECT		Reference standard +	Reference standard −	Total	
	Index test +	35	1	36	
	Index test −	3	9	12	
	Total	38	10	48	
Statistical measures	Index text: ultrasound scan Feet/ankles and knees combined Ultrasound Sensitivity: 84% (95%CI: 79%, 89%) Specificity: 60% (95%CI: 53%, 67%) Ultrasound: DC sign Sensitivity: 82% (95%CI: 76%, 88%) Specificity: 60% (95%CI: 53%, 67%)				

Reference	Singh 2021[75Singh2021]
	Ultrasound: tophus Sensitivity: 60% (95%CI: 53%, 67%) Specificity: 80% (95%CI: 74%, 86%) Index text: DECT Feet/ankles and knees combined DECT: Sensitivity: 92% (95%CI: 88%, 96%) Specificity: 90% (95%CI: 86%, 94%)
Source of funding	Supported by research funds from the Division of Rheumatology at the University of Alabama at Birmingham and the resources the use of facilities at the Birmingham VA Medical Center, Birmingham, Alabama, USA.
Limitations	Risk of bias: very high [flow and timing, reference standard protocol not described] Indirectness: included patients already diagnosed with gout
Comments	Year April 2016 to August 2019 Only 48/147 patients received the reference standard. .

Appendix E – Forest plots

E.1 Coupled sensitivity and specificity forest plots

Radiography

Figure 2: Radiography for the diagnosis of gout

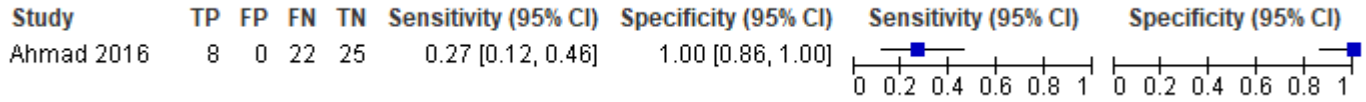
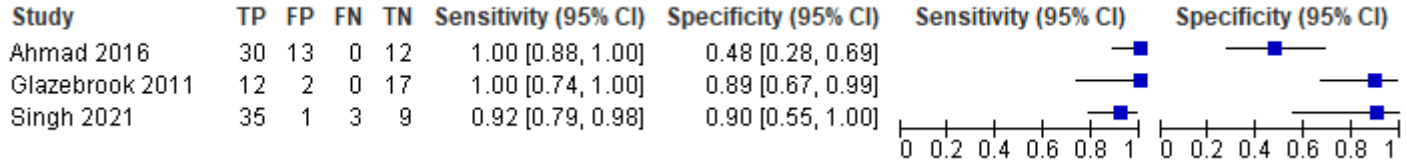


Figure 3: DECT for the diagnosis of gout



Ultrasound

Figure 4: Sensitivity and specificity of DC sign on ultrasound for gout

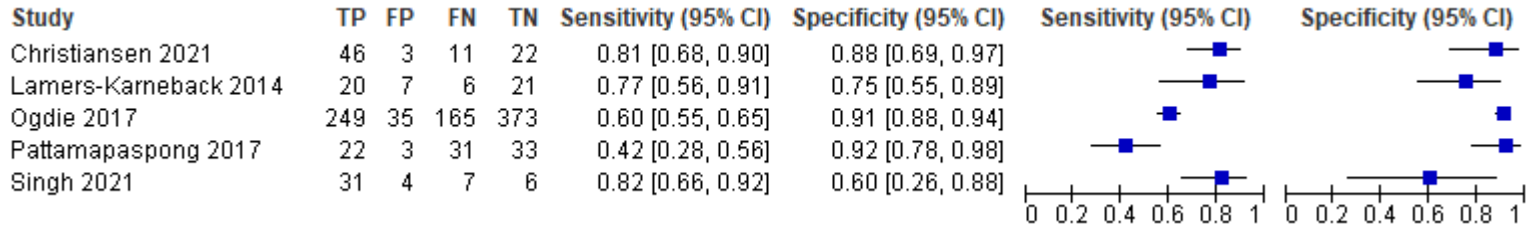


Figure 5: Sensitivity and specificity of tophi on ultrasound for gout

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christiansen 2021	45	2	12	23	0.79 [0.66, 0.89]	0.92 [0.74, 0.99]
Lamers-Karneback 2014	5	2	21	26	0.19 [0.07, 0.39]	0.93 [0.76, 0.99]
Ogdie 2017	189	21	222	387	0.46 [0.41, 0.51]	0.95 [0.92, 0.97]
Pattamapaspong 2017	21	0	32	26	0.40 [0.26, 0.54]	1.00 [0.87, 1.00]
Singh 2021	23	2	15	8	0.61 [0.43, 0.76]	0.80 [0.44, 0.97]

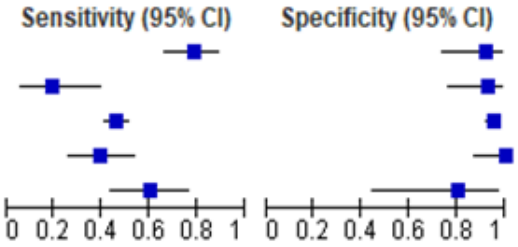


Figure 6: US: aggregates

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christiansen 2021	54	17	3	8	0.95 [0.85, 0.99]	0.32 [0.15, 0.54]
Pattamapaspong 2017	31	3	22	33	0.58 [0.44, 0.72]	0.92 [0.78, 0.98]

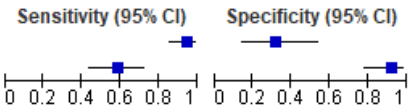


Figure 7: US: erosions

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christiansen 2021	44	11	13	14	0.77 [0.64, 0.87]	0.56 [0.35, 0.76]

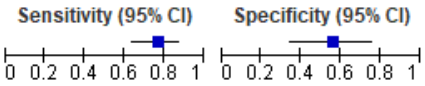


Figure 8: US: synovial hypertrophy

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christiansen 2021	56	23	1	2	0.98 [0.91, 1.00]	0.08 [0.01, 0.26]

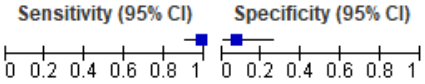


Figure 9: US: doppler activity

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christiansen 2021	56	23	1	2	0.98 [0.91, 1.00]	0.08 [0.01, 0.26]

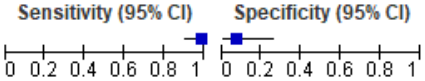
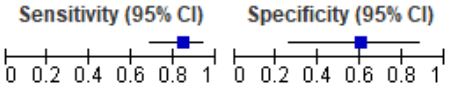


Figure 10: US: diagnosis of gout (DC sign/ tophus as per OMERACT definitions)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Singh 2021	32	4	6	6	0.84 [0.69, 0.94]	0.60 [0.26, 0.88]



Diagnostic criteria for gout not defined in the paper but DC sign and tophus as per OMERACT assessed by ultrasound in the paper.

Figure 11: US: any abnormality (DC sign/ snowstorm/ tophus)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lamers-Karneback 2014	25	9	1	19	0.96 [0.80, 1.00]	0.68 [0.48, 0.84]
Ogdie 2017	320	64	96	344	0.77 [0.73, 0.81]	0.84 [0.80, 0.88]

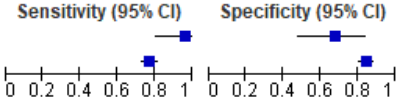


Figure 12: US: snowstorm appearance

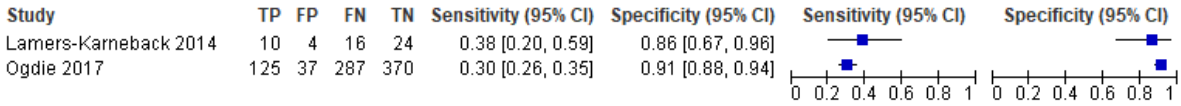


Figure 13: US: all 3 features (DC sign/aggregates/tophi)

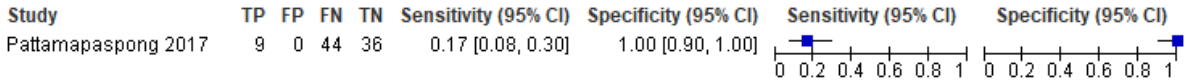


Figure 14: 2 features of gout (DC sign/ snowstorm/ tophus)

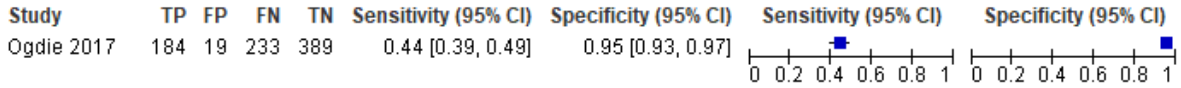


Figure 15: 3 features of gout (DC sign/ snowstorm/ tophus)

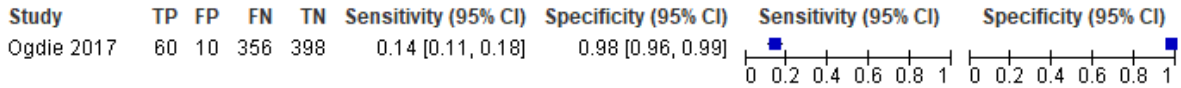


Figure 16: USS: any abnormality (DC sign/ aggregates/ tophus)

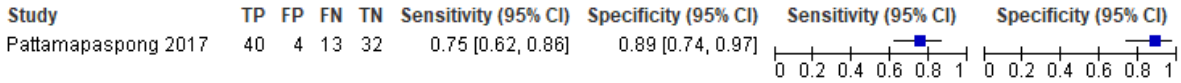


Figure 17: USS: DC sign (joints only)

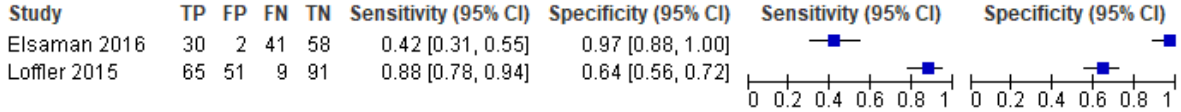


Figure 18: USS: tophi (joints only)

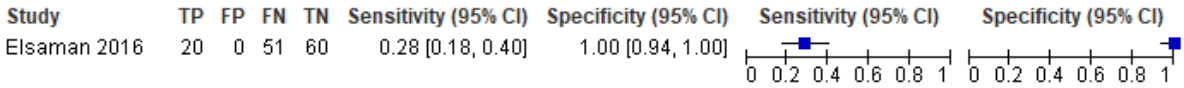


Figure 19: USS: erosions (joints only)

Figure 20: USS: diagnosis of gout (joints only). Based on one or more of the 4 sonographic signs (echogenic foci, erosions, DC signs , tophi)

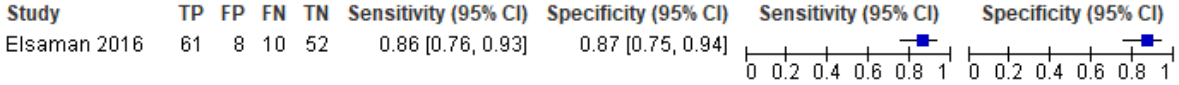


Figure 21: USS: echogenic foci (joints only)

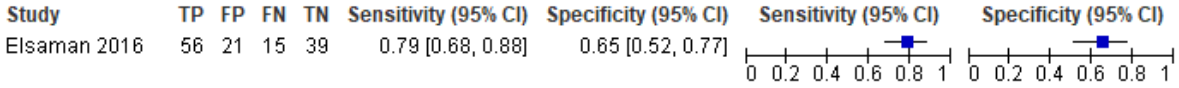


Figure 22: USS: echogenic foci + DC sign (joints only)

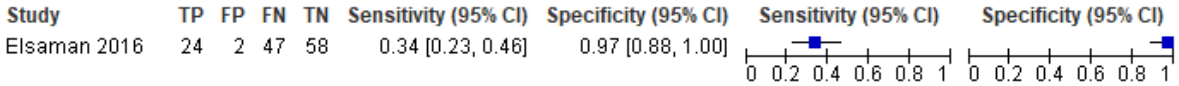


Figure 23: USS: echogenic foci +/or DC sign (joints only)

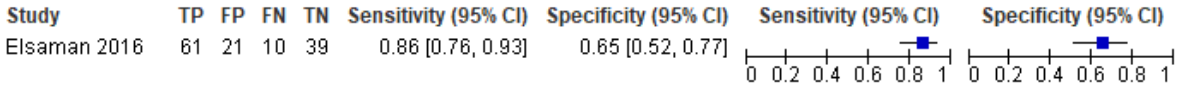


Figure 24: USS: DC sign + doppler activity (joints only)

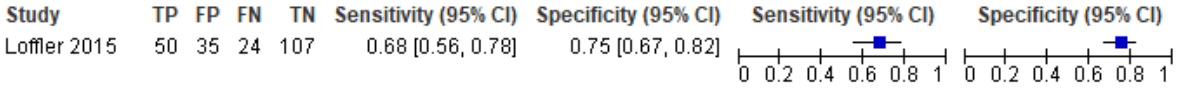
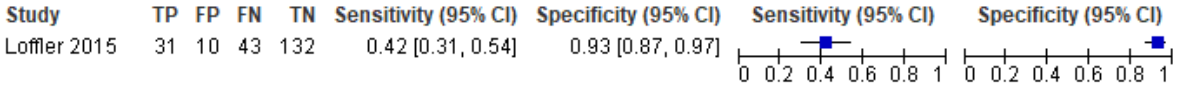
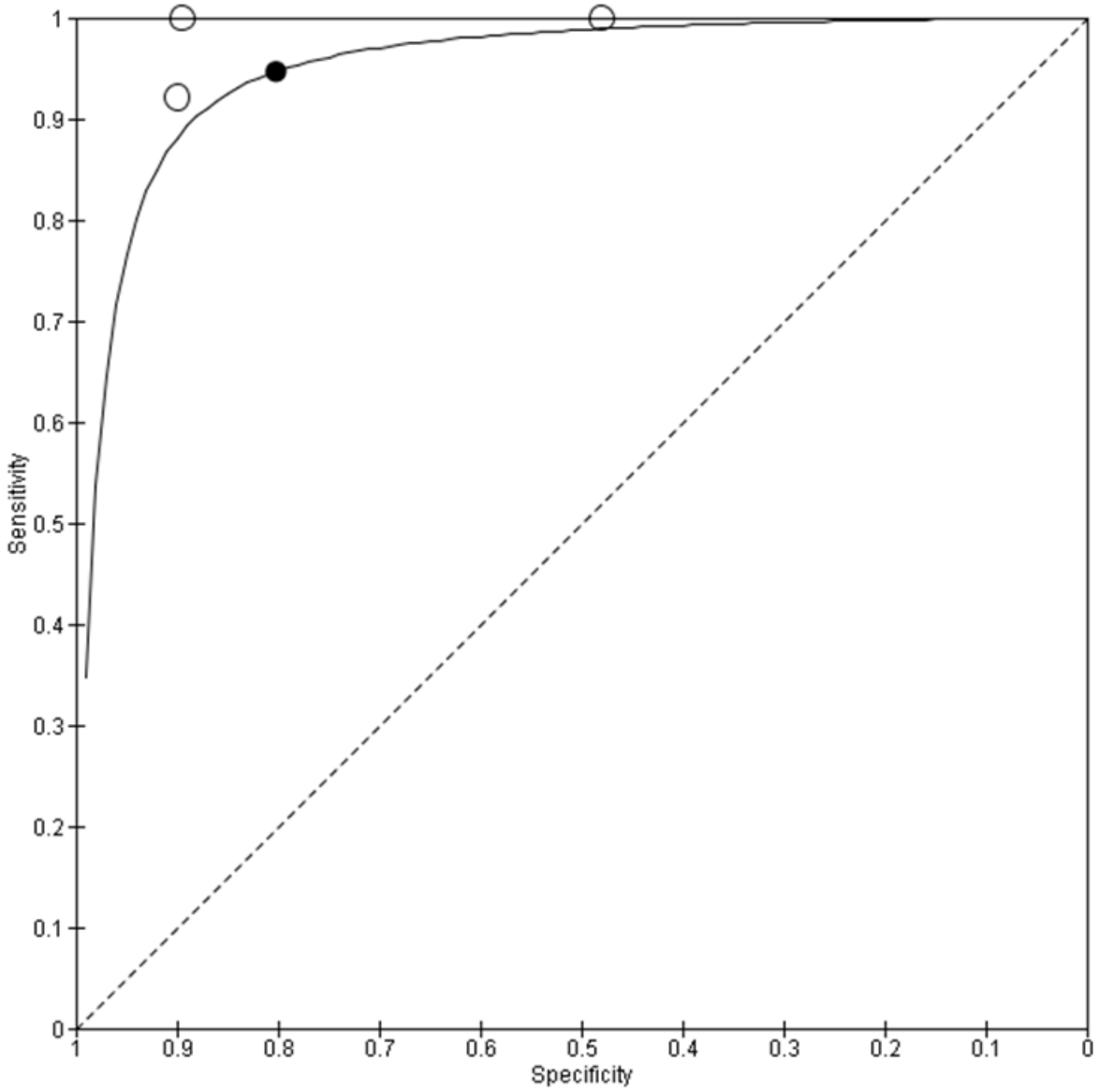


Figure 25: USS: DC sign + doppler activity + SUA (joints only)



E.2 ROC curves

Figure 26: DECT (Reference standard: joint aspiration)



Key:

Solid line represents the ROC summary curve

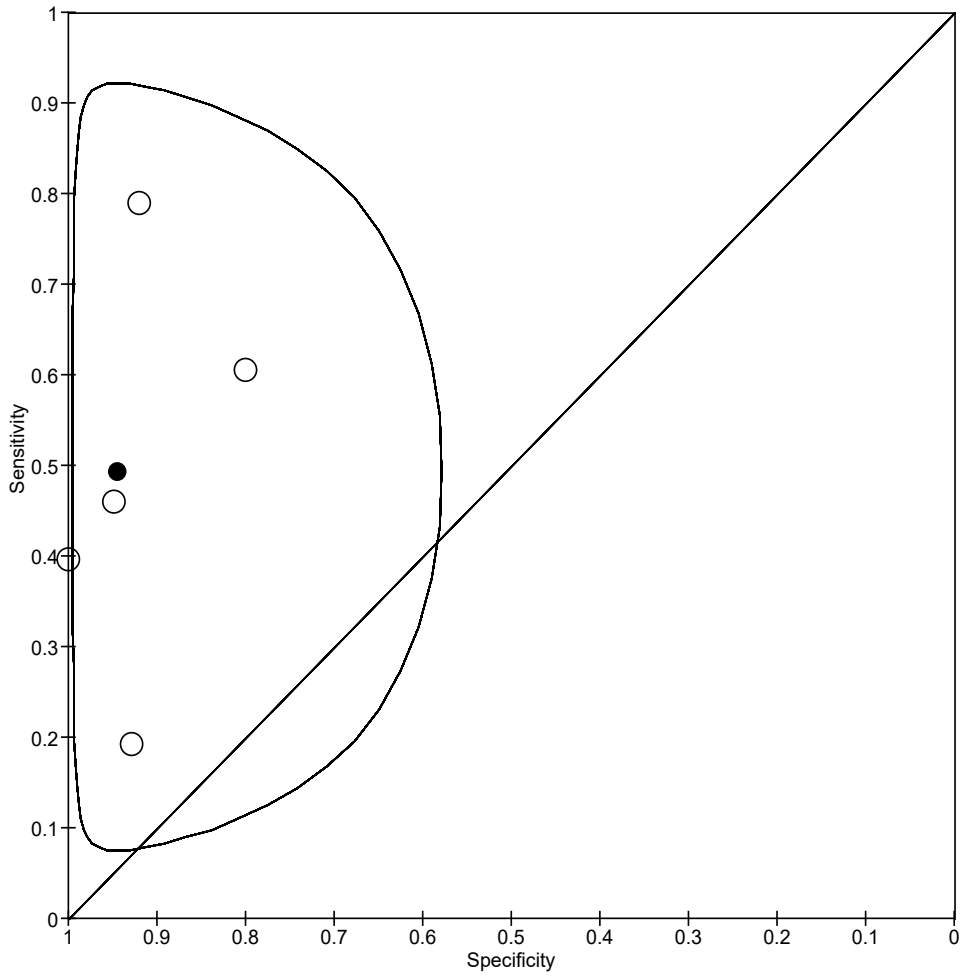
Dotted line represents the 95% confidence region of the ROC

Solid circle represents pooled ROC

Clear circles represent ROC of individual studies

Sensitivity= 0.95 (0.78-0.99); Specificity= 0.78 (0.30-0.98)

Figure 27: US: tophi (Reference standard: joint aspiration)



Key:

Solid line represents the ROC summary curve

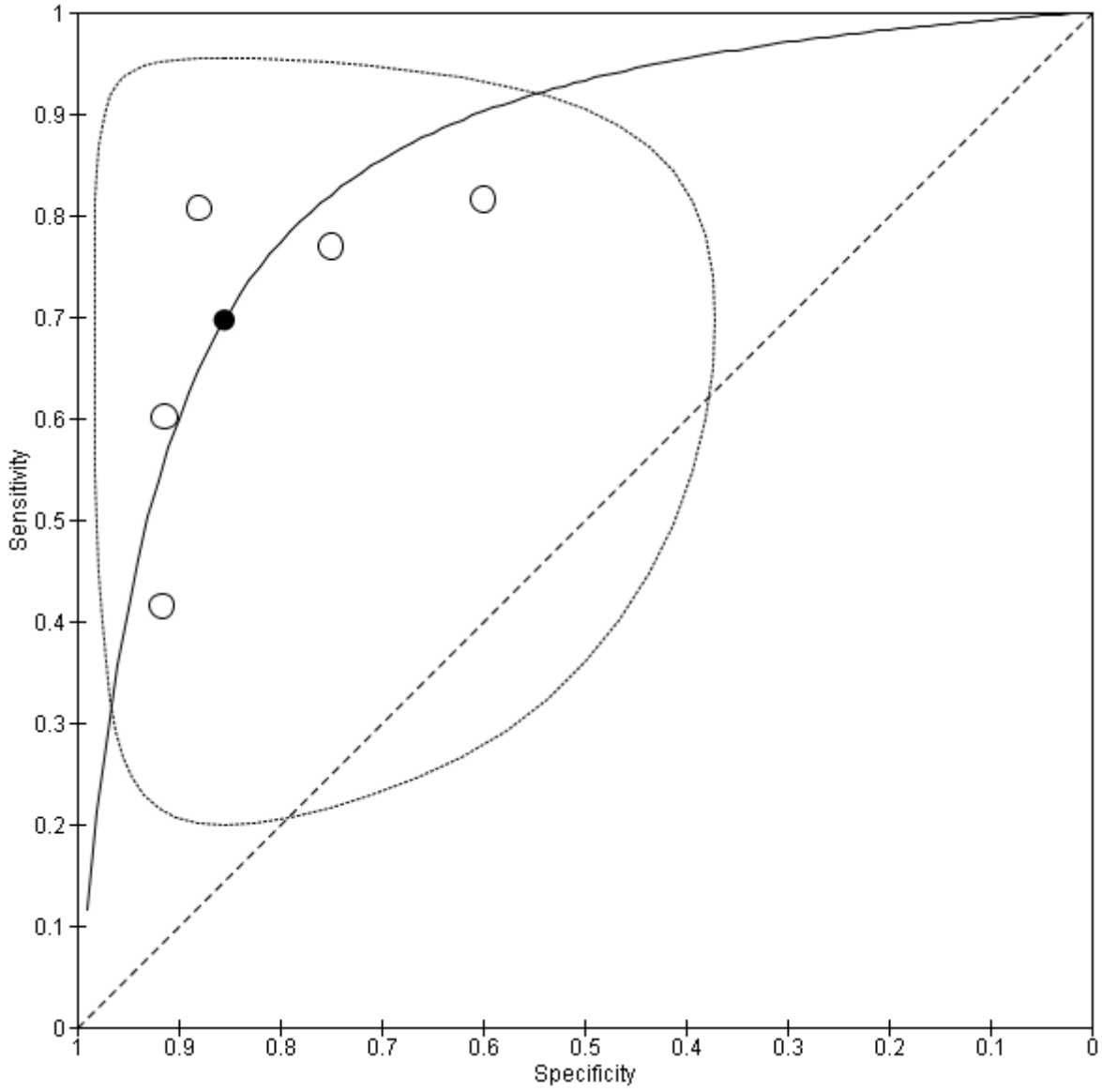
Dotted line represents the 95% confidence region of the ROC

Solid circle represents pooled ROC

Clear circles represent ROC of individual studies

Sensitivity= 0.49 (0.24-0.75); Specificity= 0.94 (0.85-0.98)

Figure 28: US: DC sign (Reference standard: joint aspiration)



Key:

Solid line represents the ROC summary curve

Dotted line represents the 95% confidence region of the ROC

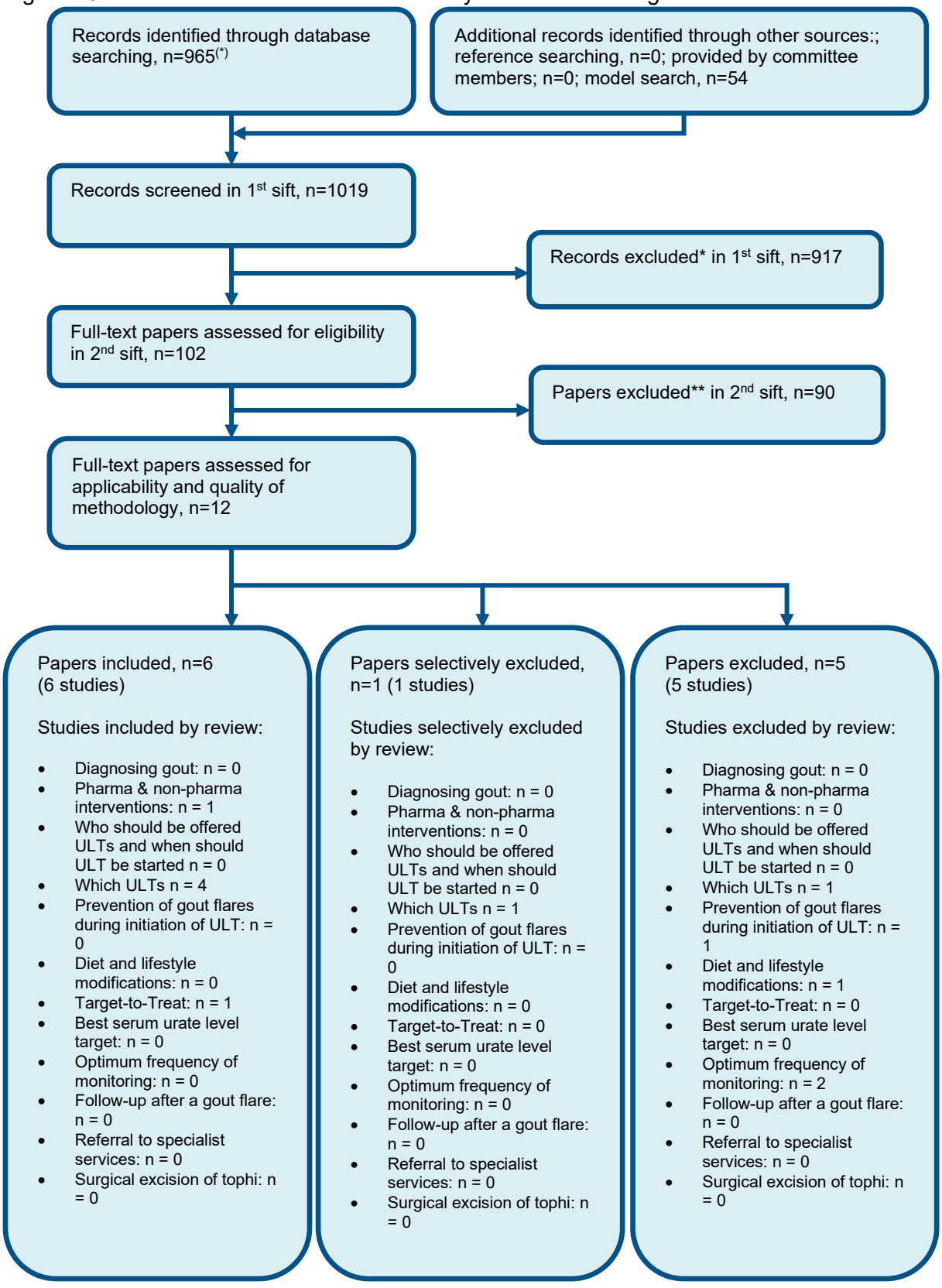
Solid circle represents pooled ROC

Clear circles represent ROC of individual studies

Sensitivity= 0.69 (0.46-0.87); Specificity= 0.86 (0.67-0.94)

Appendix F – Economic evidence study selection

Figure 29: 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 8: Studies excluded from the clinical review

Reference	
Alghamdi, 2021[2]	Incorrect study design - literature review
Baer, 2016[3]	Incorrect study design - case-control study
Bayat, 2018[4]	Systematic review but not enough details of included papers - papers checked
Bhadu, 2018[6]	Incorrect study design - case-control study, no relevant outcomes
Bongartz, 2015[7]	Incorrect study design - case-control study
Breuer, 2016[8]	No relevant outcomes
Bussieres, 2008[9]	Incorrect study design - guidelines
Cajamarca-Baron, 2021[10]	Incorrect population: systematic review of four diseases
Carotti, 2020[11]	Incorrect study design - meta-analysis
Carter, 2009[12]	Incorrect study design- not a diagnostic accuracy study
Chen, 2017[13]	Systematic review – included papers that did not match the protocol, due to study design or reference standard
Choi, 2012[40]	Incorrect study design - case-control
Choi, 2019[14]	Incorrect study design – evaluation of performance of classification criteria
Chou, 2017[15]	Incorrect study design – literature review
Chowalloor, 2013[16]	Incorrect study design - systematic review of studies with various study designs. Relevant papers checked.
Christiansen, 2018[18]	Incorrect study design - literature review
Dalbeth, 2009[19]	Incorrect study design – literature review
Dalbeth, 2016[20]	Incorrect study design – evaluation of performance of classification criteria
Das, 2017[21]	Incorrect study design - case-control
Dehlin, 2019[22]	Incorrect study design – evaluation of performance of classification criteria
Dehlin, 2015[23]	Incorrect study design – evaluation of performance of classification criteria
Expert Panel, 2017[25]	Incorrect study design - literature review of classification criteria
Filippucci, 2013[26]	Incorrect study design – not a diagnostic study
Fodor, 2014[27]	Incorrect study design - case-control
Gamala, 2020[28]	Incorrect study design – evaluation of performance of classification criteria
Gamala, 2019[29]	Incorrect study design - Systematic review and meta-analysis with various study designs
Gamez-Nava, 1998[30]	Incorrect reference standard - Rheumatologist 's opinion
Graf, 2015[32]	Incorrect study design - recommendations
Gruber, 2014[33]	No relevant outcomes (diagnostic yield only)
Gutierrez, 2013[34]	Incorrect reference standard - expert opinion
Hu, 2015[35]	Incorrect reference standard - ACR 1977 criteria
Huppertz, 2014[36]	Incorrect study design - case-control

Reference	
Janssens, 2017[37]	Incorrect study design – evaluation of performance of classification criteria
Jatuworapruk, 2016[38]	Incorrect study design – evaluation of performance of classification criteria
Jia, 2018[39]	Incorrect study design - case-control
Kravchenko, 2021[41]	Incorrect population (not all suspected gout) and incorrect intervention (not looking diagnostic procedure)
Kupfer, 2018[42]	Incorrect reference standard - grey scale CT
Lai, 2011[43]	Incorrect reference standard (MSU plus clinical and laboratory findings)
Lee, 2019[45]	Incorrect reference standard - not joint aspiration
Lee, 2017[46]	Incorrect study design - meta-analysis of studies of incorrect study design and incorrect reference standards
Lee, 2018[47]	Incorrect study design - meta-analysis of studies of incorrect design and incorrect reference standards
Liu, 2021[48]	Incorrect reference standard (clinical signs and disease duration >5 years used to diagnose gout)
Loffler, 2018[49]	Incorrect reference standard (2015 ACR/ EULAR classification- not all patients had joint aspiration)
Louthrenoo, 2017[51]	Incorrect study design – evaluation of performance of classification criteria
Malik, 2009[52]	Incorrect study design – evaluation of performance of classification criteria
Naredo, 2014[53]	Incorrect study design - case-control
Neogi, 2015[55]	Incorrect study design – evaluation of performance of classification criteria
Newberry, 2015[56]	Incorrect index test - systematic review of classification criteria
Newberry, 2017[56]	Incorrect study design – systematic review which included studies of diagnostic or classification algorithms
Norkuviene, 2015[58]	Incorrect study design - pooled results
Norkuviene, 2017[59]	Incorrect study design - case-control
Notzel, 2018[60]	Incorrect reference standard (combination of joint aspiration and DECT)
Ogdie, 2015[62]	Incorrect study designs - systematic review of case-control as well as cross-sectional studies
Ottaviani, 2012[63]	Incorrect study design - case-control
Panwar, 2018[64]	Incorrect study design – literature review
Peiteado, 2012[66]	No relevant outcomes
Perez-Ruiz, 2007[67]	Incorrect study design – literature review
Qaseem, 2017[68]	Incorrect study design - guideline
Ramon, 2018[69]	Incorrect reference standard - systematic review with incorrect reference standard in some of the studies
Rettenbacher, 2008[70]	Incorrect reference standard - included clinical and laboratory findings
Robin, 2021[71]	Incorrect comparator - association between variables and gout diagnosis
Schumacher, 2005[72]	Incorrect study design – literature review
Scirocco, 2015[73]	Incorrect study design – literature review

Reference	
Shang, 2020[74]	Incorrect study design - meta-analysis of various study designs
Sivera, 2014[76]	Systematic review - – included papers that did not match the protocol, due to study design or reference standard
Strobl, 2018[77]	Incorrect reference standard - DECT
Taylor, 2016[78]	Incorrect study design – evaluation of performance of classification criteria
Vasquez-Mellado, 2012[79]	Incorrect study design – evaluation of performance of classification criteria
Wallace, 1989[80]	Incorrect study design - correspondence
Westerfield, 2016[81]	Incorrect study design – evaluation of performance of classification crtierion
Wright, 2007[82]	Incorrect study design - case-control
Wu, 2014[83]	Incorrect reference standard - ACR criteria
Xie, 2021[84]	Incorrect study design - case-control
Xue, 2020[85]	Incorrect study design - case-control
Yu, 2018[86]	Incorrect study design - meta-analysis of various study designs
Zhang, 2020[87]	No relevant outcomes - does not report specificity
Zhang, 2018[88]	Incorrect study design - systematic review and meta-analysis of various study designs
Zhu, 2015[89]	Incorrect reference standard - not joint aspiration
Zou, 2021[90]	Incorrect reference standard - not joint aspiration

Health Economic studies

None.