# Appendix D –Diagnostic evidence

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| **Reference** | **Ahmad 2016**[1Ahmad2016] |
| **Study type** | Diagnostic accuracy study |
| **Study methodology** | Data source: not stated<br><br>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)<br><br>Gender (male to female ratio):87M/ 3F<br><br>Ethnicity: not reported<br><br>Setting: not reported<br>66/90 were in the acute stage of arthritis, 11/90 were in the inter-critical stage, 13/90 were in the chronic stage<br>Average duration of gout/ arthritis was 6.1 years<br><br>Country: India<br><br>Inclusion criteria: clinically suspected gout, based on history (especially with respect to American College of Rheumatology clinic-radiologic criteria) and serum uric acid levels.<br>Exclusion criteria: not reported |
| **Target condition(s)** | Gout |
| **Index test(s) and reference standard** | Index test: digital plain radiography<br>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.<br><br>Index test: dual-energy computed tomography |

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| **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.<br><br>Reference standard: joint aspiration<br>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.<br><br>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><br>Sensitivity for aspiration positive estimate: 27% 8/30 (95%CI: 13%, 46%)<br>Specificity for aspiration negative estimate: 100% 25/25 (95%CI: 83%, 100%)<br><br><u>Index test: DECT</u><br>Sensitivity for aspiration positive estimate: 100% 30/30 (95%CI: 86%, 100%)<br>Specificity for aspiration negative estimate: 48% 12/25 (95%CI: 28%, 68%) | | | | |
| **Source of funding** | Not reported | | | | |

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|---|---|
| **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]<br>Indirectness: none |
| **Comments** | Year: April 2011- March 2013<br>35 patients did not receive the reference standard due to an acutely painful joint.<br>Also reports sensitivity and specificity of radiography and DECT with joint aspiration plus ACR criteria as reference standard. |

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| **Reference** | **Christiansen 2021**[17Christiansen2021] |
| **Study type** | Cross-sectional |
| **Study methodology** | Data source: not reported<br><br>Recruitment: consecutive |
| **Number of patients** | n = 82 |
| **Patient characteristics** | Age, mean (range): 62.4 years (19-88 years)<br><br>Gender (male to female ratio):70M/ 12F<br><br>Ethnicity: not reported<br><br>Setting: Centre for Rheumatology and Spine Diseases<br><br>Country: Denmark<br><br>Inclusion criteria: Adults (≥18 years) referred from primary care or other hospital departments with clinical suspicion of gout.<br>Exclusion criteria: Recent (<6 weeks) glucocorticoid injection or oral glucocorticoid. |
| **Target condition(s)** | Gout |
| **Index test(s) and reference standard** | Index test: ultrasound scan<br>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] | | | | |
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| | 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.<br>The sums of all individual gout lesions across all scanned sites were calculated for each patient.<br><br>Reference standard<br>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.<br><br>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 | |

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| **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<br>Sensitivity: 81% (95%CI: 68%, 90%) 46/57<br>Specificity: 88% (95%CI: 69%, 97%) 22/25<br><br>Index text: ultrasound scan: tophi<br>Sensitivity: 79% (95%CI: 66%, 90%) 45/57<br>Specificity: 92% (95%CI: 74%, 99%) 23/25<br><br>Index text: ultrasound scan: aggregates<br>Sensitivity: 95% (95%CI: 85%, 9%) 54/57<br>Specificity: 32% (95%CI: 15%, 54%) 8/25<br><br>Index text: ultrasound scan: erosions<br>Sensitivity: 77% (95%CI: 64%, 87%) 44/57<br>Specificity: 56% (95%CI: 35%, 76%) 14/25<br><br>Index text: ultrasound scan: synovial hypertrophy<br>Sensitivity: 98% (95%CI: 91%, 100%) 56/57<br>Specificity: 8% (95%CI: 1%, 26%) 2/25<br><br>Index text: ultrasound scan: doppler activity<br>Sensitivity: 81% (95%CI: 68%, 90%) 46/57<br>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 | | | | |

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

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|---|---|
| **Reference** | **Elsaman 2016**[24Elsaman2016] |
| **Study type** | Cross-sectional |
| **Study methodology** | Data source: not stated<br><br>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)<br><br>Gender (male to female ratio):55M/ 45F<br><br>Ethnicity: not reported<br><br>Setting: ambulatory care<br><br>Country: Egypt<br><br>Inclusion criteria: undifferentiated arthritis either untreated or treated with only NSAIDs.<br>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<br>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.<br><br>Reference standard: joint aspiration<br>Polarizing light microscopy was used. Slides were usually prepared in <48 hours. |

| Reference | Elsaman 2016[24Elsaman2016] | | | | |
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| | 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 | |

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|---|---|---|---|---|---|
| **Reference** | **Elsaman 2016**[24Elsaman2016] | | | | |
| Echogenic foci+/or double contour | Total | 71 | 60 | 131 | |
| **Statistical measures** | Index text: ultrasound scan detecting gouty arthritis<br>Sensitivity for aspiration positive estimate: 85.9%<br>Specificity for aspiration negative estimate: 86.7%<br><br>Echogenic foci by US<br>Sensitivity: 78.9%<br>Specificity: 65.0%<br><br>Erosions by US<br>Sensitivity: 39.4%<br>Specificity: 61.7%<br><br>Double contour sign by US<br>Sensitivity: 42.3%<br>Specificity: 96.7%<br><br>Tophi by US<br>Sensitivity: 28.2%<br>Specificity: 100.0%<br><br>Echogenic foci + double contour<br>Sensitivity: 33.8%<br>Specificity: 96.7%<br><br>Echogenic foci +/or double contour<br>Sensitivity: 85.9%<br>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]<br>Indirectness: none |
| Comments | Diagnosis based on total number of joints, not patients.<br>All patients enrolled in the study had a BMI>23<br>Confidence intervals and prevalence not reported |

| Reference | Glazebrook 2011[31Glazebrook2011] |
|---|---|
| Study type | Retrospective cohort |
| Study methodology | Data source: not reported<br><br>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)<br><br>Gender (male to female ratio):53M/ 41F<br><br>Ethnicity: not reported<br><br>Setting: not reported<br><br>Country: USA<br><br>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.<br>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.<br>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).<br>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.<br>The first 53 patients were examined with the first generation scanner, and the remaining 41 were examined with the second-generation scanner.<br><br>Reference standard: joint aspiration<br>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.<br><br>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<br>Sensitivity for aspiration positive estimate, n=12: 100% (95%CI: 74%, 100%) for both readers<br>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]<br>Indirectness: population may not be representative as it included mainly atypical presentations of gout,</td></tr>
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| **Reference** | **Glazebrook 2011**[31Glazebrook2011] |
| **Comments** | Year 2008-2010<br>53 patients were excluded because they had enrolled in a different study. |

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|---|---|
| **Reference** | **Lamers-Karnebeck, 2014**[44 Lamers-Karnebeck2014] |
| **Study type** | Diagnostic accuracy study |
| **Study methodology** | Data source: not stated<br><br>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)<br><br>Gender (male to female ratio):MSU proven gout group: 25M/ 1F, Non MSU proven gout group: 13M/ 15F<br><br>Ethnicity: not reported<br><br>Setting: academic hospital<br><br>Country: The Netherlands<br><br>Inclusion criteria: acute mono/ oligoarthritis |
| **Target condition(s)** | Gout/ MSU arthritis |
| **Index test(s) and reference standard** | Index test: Ultrasound scan<br>An USS was performed on 6 joints: the joint with arthritis, the contralateral side, and two other joints bilaterally.<br>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.<br><br>Reference standard: joint aspiration<br>Performed on the clinically affected joint<br><br>Time between measurement of index test and reference standard: unclear |

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| **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**<br><br>**N=26** | Index text: ultrasound scan: any abnormality<br>Prevalence: in gout: 25/26<br>Prevalence in studied population: 34/54<br>Sensitivity: 96% (95% CI 95-97%)<br>Specificity: 68% (95% CI 63-73%)<br><br>Index text: ultrasound scan: double contour sign<br>Prevalence: in gout: 20/26<br>Prevalence in studied population: 27/54<br>Sensitivity: 77% (95% CI 72-81%)<br>Specificity: 75% (95% CI 66-84%)<br><br>Index text: ultrasound scan: snow-storm appearance<br>Prevalence: in gout: 10/26<br>Prevalence in studied population: 14/54<br>Sensitivity: 38% (95% CI 34-42%) | | | | |

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|---|---|
| **Reference** | **Lamers-Karnebeck, 2014**[44 Lamers-Karnebeck2014] |
| | Specificity: 86% (95% CI 83-89%)<br><br>Index text: ultrasound scan: tophus presence<br>Prevalence: in gout: 5/26<br>Prevalence in studied population: 7/54<br>Sensitivity: 19% (95% CI 17-22%)<br>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<br>Indirectness: none |
| **Comments** | Same observers for some index test and reference standard. |

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

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| **Reference** | **Loffler, 2015**[50Loffler2015] | | | | |
| **Index test(s) and reference standard** | Index test: Ultrasound scan<br>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.<br><br>Reference standard: joint aspiration<br>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.<br><br>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<br>Sensitivity: 87.8%<br>Specificity: 64.1%<br><br>Index text: ultrasound scan: DC sign/ Doppler with hypervascularization<br>Sensitivity: 67.6%<br>Specificity: 75.4%<br><br>Index text: ultrasound scan: DC sign/ Doppler with hypervascularization+ serum uric acid<br>Sensitivity: 42.0%<br>Specificity: 92.3% |
| **Source of funding** | Funding not stated |
| **Limitations** | None stated<br>Risk of bias: high for unclear reference standard blinding and unclear flow and timing<br>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] |
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| **Study type** | Cross-sectional |
| **Study methodology** | Data source: data from the Study for Updated Gout Classification Criteria (SUGAR)<br><br>Recruitment: SUGAR study recruited consecutive patients. |
| **Number of patients** | n =824 |

| Reference | Ogdie 2017[61Ogdie2017] |
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| Patient characteristics | Age, mean (SD): 60.2 years (14.6 years) for cases, 59.5 years (16.0 years) for controls<br><br>Gender (male):87% for cases, 54% for controls<br><br>Ethnicity:<br>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%<br>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%<br><br>Number of episodes<br>Cases: 1:9 %, 2-5: 22%, >5: 69%<br>Controls: 1: 23%, 2-5: 28%, >5: 49%<br><br>Previous diagnosis of gout<br>Cases: 83%<br>Controls: 28%<br><br>Current urate lowering therapy<br>Cases: 35%<br>Controls: 9%<br><br>Suspected clinical tophus<br>Cases: 36%<br>Controls: 5%<br><br>Setting: rheumatology clinics<br><br>Country: multiple countries<br><br>Inclusion criteria: ≥1 swollen joint or a subcutaneous nodule; differential diagnosis of gout. |
| Target condition(s) | Gout |

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|---|---|---|---|---|---|
| **Reference** | **Ogdie 2017**[61Ogdie2017] | | | | |
| **Index test(s) and reference standard** | Index test: ultrasound scan<br>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.<br>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.<br>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.<br><br>Reference standard: crystal based diagnosis following arthrocentesis or soft tissue nodule aspiration<br>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.<br><br>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 | |

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|---|---|---|---|---|---|
| **Reference** | **Ogdie 2017**[61Ogdie2017] | | | | |
| | Index test − | 287 | 370 | 657 | |
| | Total | 412 | 407 | 819 | |
| **Statistical measures** | Index text: ultrasound scan: any US feature<br>Sensitivity for any US feature: 76.9% (95% CI:72.6-80.9%)<br>Specificity for any US feature: 84.3% (95% CI:80.4-87.7%)<br><br>Index text: ultrasound scan: 2 US features<br>Sensitivity: 44.0% (95% CI:39.2-48.9%)<br>Specificity: 95.3% (95% CI:92.8-97.2%)<br><br>Index text: ultrasound scan: 3 US features<br>Sensitivity: 14.4% (95% CI:11.2-18.2%)<br>Specificity: 97.6% (95% CI:95.6-98.8%)<br><br>Index text: ultrasound scan: double contour sign<br>Sensitivity: 60.1% (95% CI:55.2-64.9%)<br>Specificity: 91.4% (95% CI:88.3-94.0%)<br><br>Index text: ultrasound scan: tophus<br>Sensitivity: 46.0% (95% CI:41.1-50.9%)<br>Specificity: 94.9% (95% CI:92.2-96.8%)<br><br>Index text: ultrasound scan: snowstorm<br>Sensitivity: 30.3% (95% CI:25.9-35.0%)<br>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.] | | | | |

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| **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. |

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|---|---|
| **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)<br><br>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)<br><br>Gender (male to female ratio): 60M/29F<br><br>Ethnicity: not reported<br><br>Setting: inpatients<br><br>Country:Thailand<br><br>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<br>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).<br>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.<br>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<br>Joint aspiration and an immediate microscopic examination.<br><br>Time between measurement of index test and reference standard: 2.7/ 3.6 days mean (range 0-7).<br><br>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**<br>DC sign | | Reference standard + | Reference standard − | Total | |
| | Index test + | 22 | 3 | 25 | |
| | Index test − | 31 | 33 | 64 | |
| | Total | 53 | 36 | 89 | |
| **2×2 table**<br>Intra-articular aggregates | | Reference standard + | Reference standard − | Total | |
| | Index test + | 31 | 3 | 34 | |
| | Index test − | 22 | 33 | 55 | |
| | Total | 53 | 36 | 89 | |
| 2x2 table<br>tophi | | Reference standard + | Reference standard − | Total | |
| | Index test + | 21 | 0 | 21 | |
| | Index test − | 32 | 36 | 68 | |
| | Total | 53 | 36 | 89 | |
| 2x2 table<br>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<br>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<br>Sensitivity: 42% 22/53<br>Specificity: 92% 33/36<br><br>Index text: ultrasound scan: intra-articular aggregates<br>Sensitivity: 58% 31/53<br>Specificity: 92% 33/36<br><br>Index text: ultrasound scan: tophi<br>Sensitivity: 40% 21/53<br>Specificity: 100% 36/36<br><br>Index text: ultrasound scan: any of the 3 features<br>Sensitivity: 75% 40/53<br>Specificity: 89% 32/36<br><br>Index text: ultrasound scan: all 3 features<br>Sensitivity: 17% 9/53<br>Specificity: 100% 36/36 |
| **Source of funding** | Stated to be none |
| **Limitations** | Risk of bias: serious [flow and timing, reference standard protocol not described]<br>Indirectness: included patients already diagnosed with gout/ hospitalised patients |
| **Comments** | Year January 2013-2 June 2014<br>Inpatient population<br>Retrospective study of patients with previous joint aspiration.<br>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.<br>. |

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| **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.<br><br>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)<br><br>Gender (male to female ratio): 127M/ 20F<br><br>Ethnicity: not reported<br><br>Setting: outpatient rheumatology clinic at a tertiary-care hospital<br><br>Country: France<br><br>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<br>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.<br>Analysed by one musculoskeletal radiologist who was blinded to patients' clinical features.<br>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.<br><br>Index test: ultrasound scan<br>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.<br>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. |

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|---|---|---|---|---|---|
| **Reference** | **Singh 2021**[75Singh2021] | | | | |
| | Reference standard: joint aspiration<br>Patients were classified as gout based on the presence of MSU crystals in the SFA by polarized light microscopy.<br><br>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<br>Feet/ankles and knees combined<br>Ultrasound<br>Sensitivity: 84% (95%CI: 79%, 89%)<br>Specificity: 60% (95%CI: 53%, 67%)<br><br>Ultrasound: DC sign<br>Sensitivity: 82% (95%CI: 76%, 88%)<br>Specificity: 60% (95%CI: 53%, 67%) | | | | |

| Reference | Singh 2021[75Singh2021] |
|---|---|
| | Ultrasound: tophus<br>Sensitivity: 60% (95%CI: 53%, 67%)<br>Specificity: 80% (95%CI: 74%, 86%)<br><br>Index text: DECT<br>Feet/ankles and knees combined<br>DECT:<br>Sensitivity: 92% (95%CI: 88%, 96%)<br>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]<br>Indirectness: included patients already diagnosed with gout |
| **Comments** | Year April 2016 to August 2019<br>Only 48/147 patients received the reference standard.<br>. |