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# A Delphi Exercise to Identify Characteristic Features of Gout — Opinions from Patients and Physicians, the First Stage in Developing New Classification Criteria

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*ABSTRACT.* ***Objective.*** To identify a comprehensive list of features that might discriminate between gout and other rheumatic musculoskeletal conditions, to be used subsequently for a case-control study to develop and test new classification criteria for gout.

***Methods.*** Two Delphi exercises were conducted using Web-based questionnaires: one with physicians from several countries who had an interest in gout and one with patients from New Zealand who had gout. Physicians rated a list of potentially discriminating features that were identified by literature review and expert opinion, and patients rated a list of features that they generated themselves. Agreement was defined by the RAND/UCLA disagreement index.

***Results.*** Forty-four experienced physicians and 9 patients responded to all iterations. For physicians, 71 items were identified by literature review and 15 more were suggested by physicians. The physician survey showed agreement for 26 discriminatory features and 15 as not discriminatory. The patients identified 46 features of gout, for which there was agreement on 25 items as being discriminatory and 7 items as not discriminatory.

***Conclusion.*** Patients and physicians agreed upon several key features of gout. Physicians emphasized objective findings, imaging, and patterns of symptoms, whereas patients emphasized severity, functional results, and idiographic perception of symptoms. (First Release Feb 15 2013; J Rheumatol 2013;40:498–505; doi:10.3899/jrheum.121037)

*Key Indexing Terms:*
GOUT CLASSIFICATION CRITERIA PATIENTS PHYSICIANS

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Gout is characterized by synovial and tissue deposition of monosodium urate crystals[1]. The gold standard diagnostic test for gout is the presence of monosodium urate (MSU) crystals within joint fluid or tissue and this should normally be the preferred approach to diagnosis in clinical practice[2]. However, in some research settings, examination of synovial fluid is impractical. For example, in epidemiological studies or in studies of patients recruited from primary care, there may not be access to synovial fluid microscopy. In such situations, classification criteria that aim to mimic the diagnostic gold standard are needed[3].

Classification criteria for gout that do not rely upon MSU crystal identification have previously been developed but may not be sufficiently accurate. Malik, *et al*[4] examined the validity of the non-crystal-dependent aspects of these criteria in a hospital-based population, using the gold standard of MSU crystal identification as a comparison group; they found imperfect specificity and sensitivity for the Rome, New York[5], and American Rheumatism Association (ARA)[6] criteria. Janssens, *et al* found limited accuracy of the ARA criteria, with a sensitivity of 80% and specificity of 64% in patients presenting to family practitioners with potential gout symptoms[7]. Both the Rome and New York criteria are heavily dependent on verifying the presence of tophi or MSU crystals within a joint, which is not always achievable in research settings. The rising prevalence of gout[8] and its association with the metabolic syndrome[9] and cardiovascular disease[10] make it important to study the disorder accurately. Therefore better classification criteria for gout are required.

A modification of the ARA criteria, termed the Clinical Gout Diagnosis (CGD) criteria set, was shown to have very high sensitivity (97%) and specificity (96%) in a group of rheumatology clinic patients with crystal-proven gout and other rheumatic diseases (osteoarthritis, spondyloarthritis, rheumatoid arthritis)[11]. However, the non-gout cases in that study did not undergo synovial fluid analysis and the high rate of tophi (81%) in the cohort limit the general applicability. Another novel approach based in primary care has been reported, with a positive predictive value of 80%[12]. This approach is somewhat limited by the inclusion of items associated with gout such as cardiovascular disease and male sex, rather than items intrinsic to the disease.

Traditionally, potential items for classification criteria are identified by physicians on the basis of clinical experience and knowledge of the pathology of the disease. The opinions of patients about the disease in question are rarely sought, yet patients have firsthand knowledge of how a disease is manifest and may be able to identify important clinical diagnostic pointers that could be overlooked by physicians. Patient involvement in outcome measurement[13,14], teaching health professionals[15], and self-management[16] are well described and so it was thought to be potentially useful to also include patients' perceptions regarding classification criteria in this study.

It is important to emphasize that the purpose of the overall project and for classification criteria in general is accurate case ascertainment for clinical research so that populations that are relatively homogeneous (with respect to the disease under study) are recruited. This is distinct from diagnostic criteria, which may be used for the diagnosis of individual patients in clinical practice. Nevertheless, it is usually the case that classification criteria are formed by a restricted set of items that are also used for diagnosis. In our study, we did not wish to restrict the range of items to be elicited, and thus framed questions in terms of diagnosis rather than classification, even though classification criteria are the ultimate aim. Also, in clinical practice, examination of tissue or synovial fluid is the preferred diagnostic approach for gout. In the case of rheumatology care, all rheumatologists should be able to obtain synovial fluid and examine it for the presence of MSU crystals because that is part of the training curriculum[17]. Classification criteria do not replace this diagnostic approach. Even in primary care, classification criteria do not necessarily replace the recommended diagnostic approach but can be useful aides to recalling the key features of the disease.

The objective of our study was to identify a comprehensive list of clinical, laboratory, and imaging features that could potentially discriminate between gout and other forms of arthritis or rheumatic musculoskeletal disease in a

primary healthcare setting. This study used the Delphi technique to anonymously obtain opinions from both physicians and patients, and then give them the opportunity to revise their opinion in light of the group's average. This information will serve as the basis for a planned multinational case-control study that aims to create and validate new classification criteria for the identification of gout that is designed for the setting of clinical research independent of patient care. As noted, such criteria should not be used for the diagnosis of individual patients in ordinary clinical care.

## MATERIALS AND METHODS

Eighty-one physicians from multiple countries who were interested in gout were identified from an e-mail list accumulated from previous gout studies, and 87 patients with gout were identified from patient registers at 3 New Zealand rheumatology services. Nearly all physicians were rheumatologists. Participants were asked to take part in a series of Web-based questionnaires to identify features typical of gout to be used to develop new criteria for the classification of gout. Physicians were invited by e-mail and patients were invited by letter.

Physicians were asked to rate items on the extent to which they believed that particular feature could distinguish gout from other rheumatic musculoskeletal conditions. Items presented to the physicians in the first iteration were identified by literature search and expert opinion. Any extra features identified by physicians as being important were also solicited in the first iteration. Features of gout in the patient survey were obtained from the first iteration using the question, "list as many features of gout as possible that help you and your doctor know you have gout and not some other joint condition." All participants used a 9-point rating scale (1 = not at all discriminatory; 9 = extremely discriminatory). Consensus was defined by the RAND/UCLA disagreement index whereby values > 1 indicated disagreement[18].

Items that had been suggested by physicians in the first iteration, reworded items, items for which there was disagreement, and items that had a median rating of 4–6 (uncertainty) were re-rated in the second and third iterations, if needed.

In the second iteration of the patient survey, all items from the first round were rated using the 9-point agreement scale. In the third round only the items for which there was disagreement or those with a median rating of 4–6 were re-rated. Reminders were sent by e-mail to all participants after a week of each iteration and they were given a further week to complete the survey before they were considered a nonrespondent.

According to the principles of the Delphi method[19], the participants (patients and physicians) remained anonymous to each other throughout the duration of the study. The responses to the surveys were analyzed after each round and the median and 30th and 70th percentiles were made known to each respondent in subsequent rounds. The surveys were carried out for 3 iterations or until consensus was reached, giving participants the opportunity to change their answers in light of the groups' average.

The study protocol was approved by the New Zealand Health and Disability Multiregional Ethics Committee (MEC/11/EXP/077).

## RESULTS

There were 49 respondents to the first physician survey (60% response rate). The mean age was 52.5 (SD 10.5) years, participants had been in specialist practice for 19.9 (SD 10.8) years, and consulted on a mean of 29.7 (SD 32.9) patients with gout per month. Of these, 44 responded to the second round (90%). There were 71 clinical, laboratory, and imaging features identified by literature review and expert opinion for the first iteration of the physician survey. Of these, 13 features were considered not discriminatory for gout and 25 were considered discriminatory. All 38 discriminatory and nondiscriminatory features were excluded from the second iteration. The remaining features with a median rating of 4–6 (30 items) or those for which there was disagreement (2 items) were included in the second iteration, along with 15 additional features nominated by physicians and 8 features from the first iteration for which respondents had requested clarification. There was

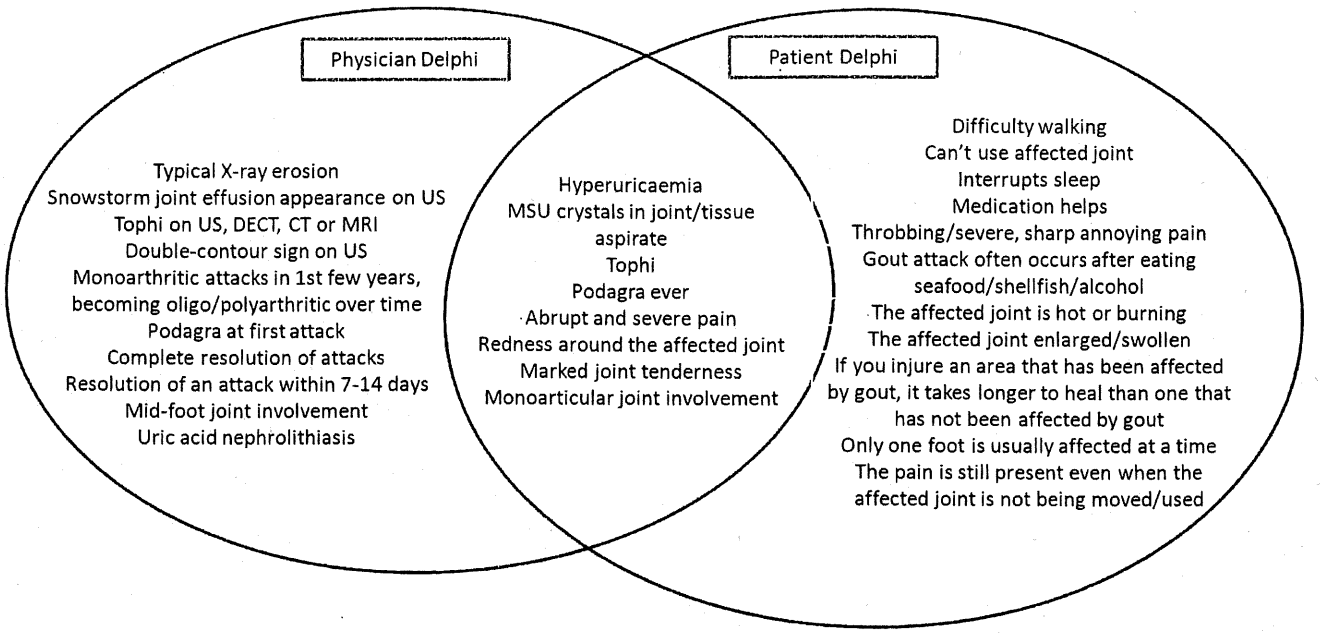


*Figure 1.* The overlap and differences among features highly rated (median 7–9) by physicians and patients. US: ultrasound; DECT: dual-energy computed tomography; CT: conventional computed tomography; MRI: magnetic resonance imaging; MSU: monosodium urate.

*Table 1.* Final ratings following the second iteration of the physician survey.

| Survey Items | Median (30th to 70th percentile)† | Disagreement Index†† |
|---|---|---|
| Items agreed by physicians to be discriminatory | | |
| MSU crystals present in joint aspirate/tissue | 9 (9 to 9) | 0 |
| Tophi (especially in typical sites such as hands, helix of the ear, olecranon bursa, and Achilles tendon) | 9 (8 to 9) | 0.13 |
| MSU crystals still present in the joint fluid despite the patient being asymptomatic | 9 (7 to 9) | 0.29 |
| Radiographic erosions with sclerotic margins and overhanging cortical edges | 8 (8 to 8) | 0 |
| First metatarsophalangeal joint (podagra) involved at the very first episode | 8 (7 to 8) | 0.16 |
| Abrupt onset of an attack that peaks around 12–24 hours | 8 (7 to 8) | 0.16 |
| Conventional CT tophi (soft-tissue masses of intermediate density) | 8 (7 to 8) | 0.16 |
| Recurrent stereotypical episodes of attacks | 8 (7 to 8) | 0.16 |
| MRI tophi (low to intermediate signal intensity on T1-weighted images) | 8 (7 to 8) | 0.16 |
| MRI tophi (variable intensity on T2-weighted images) | 8 (7 to 8) | 0.16 |
| Dual-energy CT to detect urate deposits | 8 (7 to 8) | 0.16 |
| First metatarsophalangeal joint involved ever | 7.5 (7 to 8) | 0.16 |
| US double-contour sign (hyperechoic band on the surface of articular cartilage) | 7.5 (7 to 8) | 0.16 |
| Severe pain that is maximal within 4–12 hours | 7 (7 to 8) | 0.16 |
| US tophi (hyperechoic, heterogeneous lesion surrounded by an anechoic rim) | 7 (7 to 8) | 0.16 |
| Serum uric acid elevated during the intercritical period* | 7 (7 to 8) | 0.16 |
| Attacks are monoarthritic in the first few years and become oligoarthritic and polyarthritic over time* | 7 (7 to 8) | 0.16 |
| Between attacks, the patient appears well with no signs of pain or obvious inflammation | 7 (6 to 8) | 0.37 |
| Redness/erythema around the affected joint observed by the physician | 7 (6 to 8) | 0.37 |
| Marked joint tenderness — patient protects the affected joint from use or from being knocked | 7 (6 to 7) | 0.22 |
| Monoarticular joint involvement in acute attacks | 7 (6 to 7) | 0.22 |
| Resolution of an attack within 7–14 days | 7 (6 to 7) | 0.22 |
| Raised serum urate level* | 7 (6 to 7) | 0.22 |
| Joints of the midfoot are affected, observed by the physician* | 7 (6 to 7) | 0.22 |
| Uric acid nephrolithiasis (kidney stones) | 7 (5.1 to 8) | 0.62 |
| US joint effusion (snowstorm appearance due to MSU crystals within the synovial fluid) | 7 (5 to 7) | 0.52 |
| Items agreed by physicians to be of uncertain discrimination | | |
| Patient responds rapidly to low-dose colchicine treatment* | 6.5 (6 to 7) | 0.22 |
| Swelling resolves once symptoms subside, observed by the physician | 6.5 (5 to 7) | 0.52 |
| Serum uric acid elevated during acute attack of gout* | 6.5 (5 to 7) | 0.52 |
| Warmth of skin overlying affected joint, as observed by the physician* | 6 (6 to 7) | 0.22 |
| Onset of a gout attack is generally at night* | 6 (6 to 7) | 0.22 |
| MRI erosion (a sharply marginated bone lesion with cortical bone defect)* | 6 (6 to 7) | 0.22 |
| Conventional CT to detect urate deposits* | 6 (6 to 7) | 0.22 |
| Conventional CT to detect erosion* | 6 (6 to 7) | 0.22 |
| Swelling of associated bursa, observed by the physician | 6 (5.3 to 7) | 0.42 |
| Other joints affected that are typical of gout (midfoot, ankle, knee) | 6 (5.1 to 7) | 0.48 |
| Swelling in the joint, as observed by the physician* | 6 (5 to 7) | 0.52 |
| Redness/erythema around the affected joint, as observed by the patient* | 6 (5 to 7) | 0.52 |
| Precipitation of an episode by purine-containing food (such as seafood or red meat), alcohol, dehydration, or drugs (such as diuretics) | 6 (5 to 7) | 0.52 |
| Swelling resolves once symptoms subside, as observed by the patient* | 6 (5 to 7) | 0.52 |
| Chronic uric acid nephropathy* | 6 (5 to 7) | 0.52 |
| If the patient is female she is postmenopausal* | 6 (5 to 7) | 0.52 |
| Patient is unable to wear shoes* | 6 (5 to 7) | 0.52 |
| Skin peels/scales over the affected area as acute attack is resolving* | 6 (5 to 7) | 0.52 |
| Previous diagnosis of gout made by another physician* | 6 (5 to 7) | 0.52 |
| Other joints are affected that are typical of gout such as ankle and knee, observed by the physician* | 6 (5 to 6) | 0.32 |
| Patient has a history of chronic, heavy alcohol intake* | 6 (5 to 6) | 0.32 |
| Patient is taking medication such as diuretics* | 6 (5 to 6) | 0.32 |
| Patient is a male* | 6 (5 to 6) | 0.32 |
| Patient is an organ graft recipient* | 6 (4.3 to 7) | 0.81 |
| Synovial fluid cultures of affected joint are negative for organisms (to exclude septic arthritis)* | 6 (4.3 to 6) | 0.66 |
| Family history of gout* | 5.5 (5 to 6) | 0.32 |
| Redness of skin with skip area (suggestive of gouty cellulitis), which can eliminate cellulitis (redness of skin without skip area)* | 5.5 (5 to 6) | 0.32 |
| US erosion (break in the cortical contour)* | 5 (5 to 6) | 0.32 |
| US tendon pathology (includes tenosynovitis, tendinosis, and intratendinous tophi)* | 5 (5 to 6) | 0.32 |
| Reduced renal uric acid excretion* | 5 (4.3 to 6) | 0.66 |

*Table 1.* Continued

| Survey Items | Median (30th to 70th percentile)† | Disagreement Index†† |
|---|---|---|
| Swelling of associated bursa, as observed by the patient* | 5 (4 to 6) | 0.85 |
| Warmth of skin overlying the affected joint, as observed by the patient* | 5 (4 to 6) | 0.85 |
| Asymmetric joint involvement, as observed by the physician* | 5 (4 to 6) | 0.85 |
| Patient has a high purine diet (i.e., consumes large amounts of red meat and shellfish)* | 5 (4 to 6) | 0.85 |
| Patient is obese* | 5 (4 to 6) | 0.85 |
| Patient has previously had a cardiovascular disease such as heart failure or myocardial infarction* | 5 (4 to 6) | 0.85 |
| US power Doppler signal (PWD 2–3) in monoarthritis* | 5 (4 to 6) | 0.85 |
| Elevated neutrophils within the synovial fluid* | 5 (4 to 5) | 0.32 |
| Patient is middle aged (40–50 years old)* | 5 (4 to 5) | 0.32 |
| Swelling in the joint, as observed by the patient* | 5 (3 to 6) | 0.97 |
| Elevated leukocytes within the synovial fluid* | 5 (3 to 5) | 0.52 |
| Inflammatory cells present in fluid aspirated from affected joint* | 5 (3 to 5) | 0.52 |
| Pain is relieved by joint aspiration* | 4.5 (3 to 5) | 0.52 |
| Patient also suffers from diabetes* | 4 (4 to 5) | 0.32 |
| Elevated serum C-reactive protein* | 4 (3.3 to 5) | 0.47 |
| Pain prevents walking* | 4 (3 to 5.7) | 0.81 |
| Asymmetric joint involvement, as observed by the patient* | 4 (3 to 5) | 0.52 |
| Acute uric acid nephropathy* | 4 (3 to 5) | 0.52 |
| Elevated erythrocyte sedimentation rate* | 4 (3 to 5) | 0.52 |
| Aspiration of previously affected joint shows elevated leukocyte count in joint fluid* | 4 (3 to 4) | 0.22 |
| MRI synovitis (an area of synovial compartment is enhanced with contrast, and is thicker than the width of normal synovium)* | 4 (3 to 4) | 0.22 |
| US calcium deposits (focal hyperechoic deposits within hyaline cartilage)* | 4 (3 to 4) | 0.22 |
| Items agreed by physicians to be not discriminatory | | |
| Polyarticular disease, as observed by the physician* | 3.5 (3 to 4) | 0.22 |
| Fewer than 5 joints affected | 3 (3 to 5) | 0.52 |
| Fever | 3 (3 to 5) | 0.52 |
| Polyarticular disease, observed by the patient | 3 (3 to 4) | 0.22 |
| Patient has hypertension* | 3 (3 to 4) | 0.22 |
| Functional disability (difficulty with daily activities) | 3 (2 to 5) | 0.65 |
| Loss of function of the joint (due to loss of joint motion) | 3 (2 to 4.9) | 0.62 |
| MRI cartilage pathology (focal and diffuse narrowing) | 3 (2 to 4.9) | 0.62 |
| Calcium nephrolithiasis | 3 (2 to 4) | 0.37 |
| Radiographic joint space abnormalities (includes widening, narrowing, and ankylosis) | 3 (2 to 4) | 0.37 |
| Patient complains of flu-like symptoms | 3 (1.1 to 4) | 0.48 |
| Malaise | 3 (1.1 to 4) | 0.48 |
| Elevated platelet count | 2 (1.1 to 4) | 0.48 |
| Early morning stiffness lasting > 30 minutes | 2 (1 to 2.9) | 0.27 |
| Spinal involvement | 2 (1 to 2) | 0.13 |

* Rating from final iteration. † Values of 1–3.5 indicate the item was considered not discriminatory for gout, 4–6.5 as uncertain, and 7–9 as discriminatory for gout. †† Disagreement index > 1 indicates disagreement[18]. US: ultrasound; CR: conventional radiology; CT: computed tomography; MRI: magnetic resonance imaging; MSU: monosodium urate.

agreement on all items during the second iteration so that a third iteration was not required. The final list of features (Table 1) contained 4 additional discriminatory items and 2 additional nondiscriminatory items. There were 52 items that were rated as uncertain (median rating 4–6).

There were 14 respondents to the first patient survey (16% response rate). Of these, 13 (93%) responded to the second iteration and 9 (69%) to the third iteration. Patients were a median age of 63 (range 38–89) years and the median duration of disease was 10 (range 4–25) years. In the first round, 46 features were identified by patients. In the second round, it was agreed that 2 of the features were not discriminatory for gout and that 22 of the features were discriminatory. Patients were uncertain of the diagnostic importance of 19 of the features or were in disagreement concerning 3 items and these were re-rated in the final iteration. After the final iteration of the patient survey (Table 2) there was agreement that 7 items were not discriminatory for gout, 25 items were discriminatory for gout, and 14 items were rated with uncertainty or disagreement.

Comparison of the patient and physician data showed consensus on the following general characteristics thought to be specific for gout: the suddenness of onset, redness and swelling of the affected joint, the marked tenderness of the joint, elevated serum urate levels, presence of tophi, the presence of MSU crystals in synovial fluid, and involvement of the first metatarsophalangeal joint (Figure 1).

*Table 2.* Final ratings following the third iteration of the patient survey.

| Survey Items | Median (30th to 70th percentile) Rating† | Disagreement Index†† |
|---|---|---|
| Items agreed by patients as being discriminatory | | |
| Blood test shows an increase in uric acid in the blood | 9 (9 to 9) | 0 |
| During an attack of gout the pain is so bad you find it hard to walk | 9 (9 to 9) | 0 |
| During an attack of gout you cannot use the affected joint | 9 (8.6 to 9) | 0.05 |
| During an attack of gout the pain is so bad it interrupts your sleep | 9 (8.2 to 9) | 0.1 |
| During an attack of gout the joint is so sensitive you cannot even sleep with a sheet touching the affected area | 9 (7.2 to 9) | 0.26 |
| Medication such as indomethacin, allopurinol, or colchicine keeps the gout attacks at bay | 9 (6.6 to 9) | 0.37 |
| The pain is of a throbbing type | 9 (5.6 to 9) | 0.59 |
| Presence of crystals from joint fluid under a microscope | 9 (5.6 to 9) | 0.59 |
| An attack of gout often occurs after eating seafood/shellfish* | 8 (7 to 9) | 0.29 |
| Onset of an attack is sudden | 8 (6.6 to 9) | 0.37 |
| The big toe is affected | 8 (6 to 9) | 0.49 |
| The affected joint is hot | 8 (5.6 to 9) | 0.59 |
| The affected joint is red | 8 (5.6 to 9) | 0.59 |
| Tophi (lumps) are present in areas such as the elbows, fingers, and toes | 8 (5 to 9) | 0.75 |
| The pain is annoying | 8 (4.2 to 8.4) | 0.98 |
| A flare-up of an attack of gout responds rapidly to medication such as prednisone or naproxen | 7 (7 to 7.8) | 0.13 |
| The affected area is very sensitive to touch | 7 (6.2 to 9) | 0.45 |
| The affected joint is swollen | 7 (6 to 9) | 0.49 |
| An attack of gout often occurs after consuming alcohol* | 7 (6 to 8.6) | 0.45 |
| Severe, sharp pain in the affected joint | 7 (5.6 to 9) | 0.59 |
| The affected joint is enlarged | 7 (5.6 to 8) | 0.48 |
| If you injure an area that has been affected by gout, it takes longer to heal than one that has not been affected by gout* | 7 (5 to 9) | 0.75 |
| Only one foot is usually affected at a time | 7 (5 to 9) | 0.75 |
| The pain is still present even when the affected joint is not being moved/used | 7 (5 to 9) | 0.75 |
| There is a burning feeling in the affected area | 7 (4.6 to 8.4) | 0.83 |
| Items agreed to be uncertain | | |
| An attack of gout often occurs after eating red meat* | 6 (5.4 to 7.2) | 0.42 |
| An increase in blood pressure may be observed* | 5 (5 to 7.8) | 0.63 |
| Other members of your family have/have had gout* | 5 (5 to 6.6) | 0.45 |
| The duration of an attack of gout is relatively short (1–2 days)* | 5 (4.4 to 6.6) | 0.71 |
| Items agreed to be not discriminatory | | |
| The affected joints appear deformed/have changed shape* | 3 (2.4 to 5) | 0.6 |
| The elbows are affected* | 3 (1.8 to 5) | 0.67 |
| The ball of the foot is affected* | 3 (1.4 to 5.6) | 0.91 |
| The fingers are affected* | 3 (1.4 to 4.2) | 0.5 |
| An attack of gout often occurs after eating asparagus | 3 (1 to 5) | 0.75 |
| The knees are affected* | 3 (1 to 4.2) | 0.54 |
| The pain is always present in the hands — even in the absence of an attack of gout | 1 (1 to 5) | 0.75 |
| Items for which there was disagreement | | |
| The pain may produce depression* | 7 (4 to 9) | 1.09 |
| The joints in the middle of the foot are affected* | 4 (2.4 to 6.2) | 1.12 |
| White lumps are observed on the fingers* | 5 (3.8 to 8) | 1.14 |
| The area around the affected joint is swollen* | 8 (3.8 to 9) | 1.17 |
| The pain is worse when you move the affected joint* | 5 (3.4 to 8.6) | 1.35 |
| When these lumps are lanced they release a white substance* | 1 (1 to 6.8) | 1.45 |
| Friction/rubbing makes the affected joint more painful* | 5 (1.8 to 6.8) | 1.47 |
| The attack resolves quickly* | 5 (2.4 to 7) | 1.64 |
| The affected joint is stiff* | 3 (1.8 to 7.6) | 2.07 |
| The ankles are affected* | 5 (2.4 to 7.6) | 2.21 |

* Item re-rated during the third iteration. † Values of 1–3.5 indicate the item was considered not discriminatory for gout, 4–6.5 as uncertain, and 7–9 as discriminatory for gout. †† Disagreement index > 1 indicates disagreement[18].

## DISCUSSION

This Delphi exercise identified 26 features of gout that expert physicians believed were potentially appropriate to distinguish gout from other rheumatic musculoskeletal diseases. Patients with chronic gout further supported these findings by identifying many of the same features as physicians.

One difference between patients and physicians was the

different emphasis on functional disability. Patients believed that the inability to carry out everyday tasks such as walking was an important diagnostic feature and rated it highly whereas physicians believed that it was not at all discriminatory. There was more emphasis by patients on the severity of the symptoms of gout such as red, hot, swollen, and tender joints that prevent sleep and normal everyday functioning. The response to treatment and the triggers for gout attacks were also seen by patients to be more important than physicians. In contrast, physicians tended to emphasize imaging, the pattern of joint involvement, and its behavior over time. Overall, physicians were more focused on diagnostic criteria and patients on disease severity criteria.

There was greater disagreement among patients regarding the specificity of features they suggested, compared to among physicians. This is consistent with substantial interindividual variation in how diseases manifest and how symptoms are interpreted by patients. Physicians are trained to recognize nomothetic commonalities, patterns, symptom clusters, and pathology, rather than idiographic variations of symptoms. An obvious key difference between patients and physicians that is relevant here is that physicians have experience in distinguishing between different rheumatic diseases, whereas patients have experience only in distinguishing between having and not having gout, and may not be able to easily determine when symptoms are due to gout and not some other rheumatic disease.

Many of the items for which there was agreement between patients and physicians already appear within existing classification criteria. This is not surprising, since such features are likely to be highly typical or characteristic of the disease. An improvement upon existing criteria may still be achievable with different criteria formats (for example, weighting of different features) and inclusion of new items (for example, modern imaging techniques).

Unfortunately, the patient response rate in our study was much lower than expected. Five patients did not complete all iterations and thus were considered nonrespondents, we received 8 "return to sender" letters due to incorrect addresses, and we received at least 1 letter and some telephone messages from patients who wanted to participate but had no access to a computer. But the reason for nonresponse was unknown for most nonrespondents. In light of the low response rate, the patient results cannot be considered representative of the gout patient population. In addition, the patients reported features such as tophi that may occur only in more severely affected patients. Also, it should be noted that all patient participants were from New Zealand whereas the physicians were from several countries. It would be of interest to obtain opinions from a larger number of patients from different countries. Finally, patients and physicians were hospital-based rather than recruited from primary care settings, which may tend to bias opinion toward more severe gout. Overall, it should not be considered that the patients in our study were representative of the gout population. Nonetheless, their opinions are of value.

This Delphi consensus methodology has provided some direction toward features that could be tested for possible new gout classification criteria. The next phase of this project is to conduct a case-control study to establish the most accurate combinations of these features for classifying gout when compared to the gold standard diagnostic procedure of MSU identification in tissue or synovial fluid.

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**A Delphi Exercise to Identify Characteristic Features of Gout — Opinions from Patients and Physicians, the First Stage in Developing New Classification Criteria**

Prowse RL, Dalbeth N, Kavanaugh A, Adebajo AO, Gaffo AL, Terkeltaub R, Mandell BF, Suryana BP, Goldenstein-Schainberg C, Diaz-Torne C, Khanna D, Lioté F, McCarthy G, Kerr GS, Yamanaka H, Janssens H, Baraf HF, Chen JH, Vazquez-Mellado J, Harrold LR, Stamp LK, Van De Laar MA, Janssen M, Doherty M, Boers M, Edwards NL, Gow P, Chapman P, Khanna P, Helliwell PS, Grainger R, Schumacher HR, Neogi T, Jansen TL, Louthrenoo W, Sivera F, Taylor WJ. A Delphi exercise to identify characteristic features of gout — opinions from patients and physicians, the first stage in developing new classification criteria. J Rheumatol 2013;40:498-505. The following name should be added to the author list: Rieke Alten (MD, PhD, Department of Internal Medicine, Rheumatology, Clinical Immunology, Schlosspark-Klinik, Teaching Hospital, Charité University Medicine, Berlin, Germany). We regret the error. doi:10.3899/jrheum.121037.C1

Concise report

# A modified Delphi exercise to determine the extent of consensus with OMERACT outcome domains for studies of acute and chronic gout

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## ABSTRACT

**Objectives:** To reach consensus with recommendations made by an OMERACT Special Interest Group (SIG).

**Methods:** Rheumatologists and industry representatives interested in gout rated and clarified, in three iterations, the importance of domains proposed by the OMERACT SIG for use in acute and chronic gout intervention studies. Consensus was defined as a value of less than 1 of the UCLA/RAND disagreement index.

**Results:** There were 33 respondents (61% response rate); all agreed the initial items were necessary, except "total body urate pool". Additional domains were suggested and clarification sought for defining "joint inflammation" and "musculoskeletal function". Items that demonstrated no clear decision were re-rated in the final iteration. There were six highly rated items (rating 1–2) with four slightly lower rating items (rating 3) for acute gout; and 11 highly rated items with eight slightly lower ratings for chronic gout.

**Conclusions:** Consensus is that the following domains be considered mandatory for acute gout studies: pain, joint swelling, joint tenderness, patient global, physician global, functional disability; and for chronic gout studies: serum urate, gout flares, tophus regression, health-related quality of life, functional disability, pain, patient global, physician global, work disability and joint inflammation. Several additional domains were considered discretionary.

Gout is a systemic metabolic disease manifested by hyperuricaemia, acute and chronic arthritis, monosodium urate crystal deposits in connective tissue producing tophi, and uric acid nephrolithiasis. It is the most common inflammatory arthritis in men. It may be associated with the metabolic syndrome and with an increased risk of cardiovascular disease.

There has been renewed interest in the treatment of gout with recent reported intervention studies of new agents, including etoricoxib,[1] lumiracoxib[2] in acute gout or attacks of gout and febuxostat,[3] pegylated-uricase[4] in chronic gout. These studies have highlighted the relative paucity of validated outcome measures with which to judge efficacy. Gout has been discussed at OMERACT 7[5] and OMERACT 8[6] and a preliminary list of relevant domains has been developed by a Special Interest Group (SIG). These domains include: pain, inflammation, function, patient global, safety for acute gout studies; serum urate, gout flare recurrence, tophus regression, joint damage imaging, health-related quality of life (HRQOL), musculoskeletal function, patient global assessment, participation, safety and tolerability for chronic gout studies. A key aim of treatment for chronic gout is likely to include elimination of the deposited urate crystals.

The purpose of this study was to formally determine the extent of consensus with these recommendations using a Delphi approach. This technique iteratively and anonymously solicits opinions from participants, who have the opportunity to revise their opinion in the light of feedback on the opinion of the group as a whole.[7]

## METHODS

Fifty-four rheumatologists and industry representatives interested in gout were identified from the OMERACT Gout mailing list and a previous Delphi exercise that examined the question of gout flare.[8] Respondents were asked to rate the importance of measuring domains in acute gout and chronic gout intervention studies on a seven-point scale (1 = definitely necessary to 7 = definitely not necessary), using a web-based questionnaire. Studies for acute gout refer to interventions that aim to limit the severity or duration of an acute gout flare. The precise definition of acute gout or gout flare is the subject of an ongoing study under the OMERACT umbrella.[9] Studies for chronic gout refer to interventions that aim to prevent recurrent episodes of acute gout or limit the overall impact of persistent symptoms, disease activity or functional consequences of persistent disease over an extended time period. The domains suggested by the OMERACT SIG were used for the first iteration, supplemented by domains of "physician global assessment" and "work disability" for acute gout and "work disability", "physician global assessment", "joint inflammation", "pain" and "total body urate pool" for chronic gout studies. These extra domains were selected on the basis of literature review and expert opinion. Additional domains felt to be of importance were also solicited from Delphi respondents. Consensus was defined by the UCLA/RAND disagreement index, whereby values of less than 1 indicated agreement.[10] This index is essentially calculated from the 30th and



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70th percentile of the respondents' ratings, adjusted for symmetry between the central point of the interpercentile range and the mid-point of the rating scale. The adjustment factor was derived from experimental work that compared different definitions of what constituted "disagreement" among panels of various sizes.

New items, re-worded items, and items for which there was disagreement and/or median rating of 4 (neither agreement nor disagreement) were re-rated in the second iteration. In the final (third) iteration, no new items were introduced and only items for which there was disagreement and/or median rating of 4 were re-rated. Reminders were emailed at 2 weeks following the start of each round and potential respondents were given a further week to respond before being declared a non-respondent.

According to the principles of the Delphi technique,[7] respondents were not known to each other during the survey and the group response (median and interpercentile range) was made known to respondents at the time any item was rated for a second or third time.

The study protocol was reviewed by the New Zealand Health and Disability Central Region Ethics Committee.

## RESULTS

There were 33 respondents (61% response rate) to the first survey; 54% were from North America, 18% from Europe and 27% from Asia-Pacific. Of these, 29 (88%) responded to the second and third rounds of the survey. There were three participants from industry, all of whom had first-hand knowledge of design and conduct of pharmaceutical trials in gout.

All initial items were agreed as important (median rating 1–3), except for "total body urate pool" (median rating 4). Additional domains were suggested and clarification sought for the meaning of "joint inflammation" and "musculoskeletal function". Subsequently the new items and "total body urate pool" were (re)rated in the second and third (final) iteration.

For acute gout (table 1) the final list contained six items (median rating 1–2) and four items (median rating 3); and for chronic gout 11 items (median rating 1–2) and eight items (median rating 4) (table 2). Additional domains that this group of respondents felt were important for studies of chronic gout were health care utilisation, costs, patient utilities and comorbidities. Functional status should be assessed in terms of joint function (range of motion), activity limitation (disability) and participation restriction. It remained unclear whether an acute phase marker should be a core domain for studies of chronic gout.

## DISCUSSION

This Delphi exercise has confirmed that the domains identified by the OMERACT SIG are important for studies of acute and chronic gout. However, additional domains were also seen as important, creating a list of outcome areas that might be too unwieldy for clinical trials. In addition, this exercise has clarified the meaning of "function" and "inflammation" listed in the OMERACT SIG recommendation, creating further domains. It is important to emphasise that identification of monosodium urate crystals was not considered sufficiently important by participants to be included in the final list, probably as it was a necessary prerequisite that the recommendations only applied to patients who had a confirmed diagnosis of gout.

One approach to resolving the tension between practical feasibility and desire to measure everything that is relevant, is to consider listing some items as mandatory for clinical trials and some items as discretionary (while still being seen as important). This approach has been successful for psoriatic arthritis,[11] lupus,[12] osteoporosis[13] and osteoarthritis.[14] Based on the results from this Delphi exercise, it is proposed that outcome domains for gout studies be organised into the groups shown in fig 1, and that this proposal be formally ratified at the OMERACT 9

**Table 1** Final ratings for outcome domains in studies of acute gout

| | Median rating (30th to 70th percentiles)‡ | Disagreement index§ |
|---|---|---|
| Pain* | 1 (1 to 1) | 0 |
| Patient global* | 2 (1 to 2) | 0.22 |
| Physician global | 2 (2 to 3) | 0.32 |
| Work disability (absentee-ism or presentee-ism) | 3 (2 to 3) | 0.32 |
| Inflammation of joint*† | | |
| Joint erythema | 3 (2 to 3) | 0.32 |
| Joint tenderness | 1 (1 to 2) | 0.22 |
| Joint swelling | 1 (1 to 2) | 0.22 |
| Acute phase marker | 3 (2 to 4) | 0.85 |
| Function*† | | |
| Functional disability (difficulty with daily activities) | 2 (1 to 3) | 0.52 |
| Joint impairment (loss of joint motion) | 3 (2 to 4) | 0.85 |

*Items recommended by OMERACT SIG.
†These two items were rated highly in the first iteration (median 1) but respondents requested more precise clarification of meaning for subsequent iterations.
‡Ratings of 1–3 indicate item should be included in studies of gout; 4 indicates uncertainty; 5–7 indicate item should not be included in studies of gout.
§A disagreement index of less than 1 indicates no disagreement.[10]

**Table 2** Final ratings for outcome domains in studies of chronic gout

| | Median rating (30th to 70th percentiles)‡ | Disagreement index§ |
|---|---|---|
| Adverse effects of intervention* | 1 (1 to 2) | 0.22 |
| Serum urate* | 1 (1 to 1) | 0 |
| Gout flare recurrence* | 1 (1 to 1) | 0 |
| Tophus regression* | 2 (2 to 2) | 0 |
| Health-related quality of life* | 2 (1.6 to 3) | 0.41 |
| Pain | 2 (1 to 2.4) | 0.33 |
| Patient global* | 2 (1 to 2) | 0.22 |
| Physician global | 2 (1 to 3) | 0.52 |
| Work disability (absentee-ism or presentee-ism) | 2 (2 to 3) | 0.32 |
| Joint inflammation | 2 (2 to 4) | 0.85 |
| Physical function*† | | |
| Functional disability (difficulty with daily activities) | 2 (1 to 3) | 0.52 |
| Joint impairment (loss of joint motion) | 3 (2 to 3) | 0.32 |
| Joint damage imaging* | 3 (3 to 4) | 0.32 |
| Participation (life-role)* | 3 (2 to 4) | 0.85 |
| Health care utilisation | 3 (3 to 3) | 0 |
| Costs | 3 (3 to 4) | 0.32 |
| Patient utility (value of current health state) | 3 (2 to 3) | 0.32 |
| Comorbidities | 3 (2 to 4) | 0.85 |
| Acute phase marker | 4 (3 to 5) | 0.52 |
| Total body urate pool | 5 (3.4 to 6) | 0.53 |
| Impact on family | 5 (4 to 6) | 0.37 |
| Absence of urate crystals from knee synovial fluid | 5 (4 to 6) | 0.37 |
| Depression | 6 (4 to 6) | 0.37 |

*Domain recommended by OMERACT SIG.
†This item was rated highly in the first iteration (median 2) but respondents requested more precise clarification of meaning for subsequent iterations.
‡Ratings of 1–3 indicate item should be included in studies of gout; 4 indicates uncertainty; 5–7 indicate item should not be included in studies of gout.
§A disagreement index of less than 1 indicates no disagreement.[10]

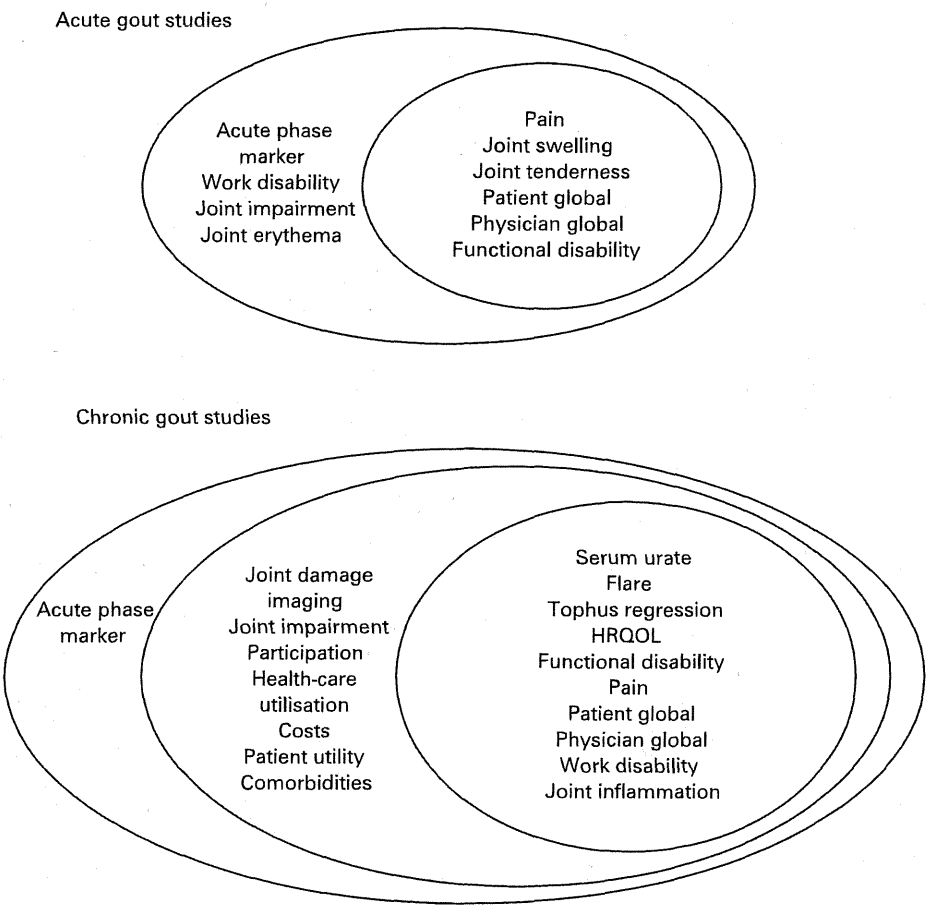


**Figure 1** Proposed domains for gout studies. Items within inner ellipse are considered mandatory, within the next ellipse as discretionary and within the outermost ellipse as for further research.

meeting during 2008. Domains that scored a median of 1 or 2 were placed in the inner ellipse, domains that scored a median of 3 into the next ellipse and those that scored a median of 4 into the outermost ellipse. For all studies, it is mandated that safety and tolerability of investigational products also be assessed. Once core domains are agreed, a subsequent task is to identify or develop appropriate tools to measure each domain.

This exercise could be combined with the development of core sets for the International Classification of Functioning, Disability and Health (ICF), where core sets projects aim to identify those factors important for specific health states, including personal perspectives on activities and participation to complement the views of health professionals.[15]

It is important to recognise that the method or instrument to measure these domains was not addressed in this Delphi exercise. In particular, the rating of the importance of the domain by respondents reflected their own expert judgement, rather than the extent to which the domain could be measured in a way that satisfies the OMERACT filter (truth, discrimination, feasibility).[16] Specific outcome measures used in clinical trials of gout treatment were reviewed recently. This review describes currently used measures in terms of the OMERACT filter.[9] Other studies that address the measurement properties of instruments for some of these domains are currently in progress. It may be necessary to modify fig 1 in light of currently available tools for outcome measurement in gout, and this is likely to be a key area of discussion at the OMERACT 9 meeting. Even so, this Delphi exercise does point the way to where researchers should focus attention on producing validated outcome tools for gout studies.

A further limitation to this study is represented by the selected group of Delphi participants and non-response rate. This might limit the validity of the final recommendations; in particular, patients with gout were not invited to participate in this exercise. None the less, the initial response rate was actually very satisfactory in comparison with other similar Delphi exercises and the very broad geographical coverage of the panel does suggest adequate international representation.

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