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Gout Classification Criteria: Update and Implications

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Abstract Gout is the most common inflammatory arthritis, with a rising prevalence and incidence worldwide. There has been a resurgence in gout research, fueled, in part, by a number of advances in pharmacologic therapy for gout. The conduct of clinical trials and other observational research in gout requires a standardized and validated means of assembling well-defined groups of patients with gout for such research purposes. Recently, an international collaborative effort that involved a data-driven process with state-of-the art methodology supported by the American College of Rheumatology and the European League Against Rheumatism led to publication of new gout classification criteria.

Keywords Gout · Classification criteria · Conjoint analysis

Introduction

Despite being one of the most common rheumatic diseases, gout had received little research attention for many years, partly due to a common perception that it is a well-understood disease, easily diagnosed and treated, and often resulting from dietary and lifestyle excesses [1]. The increasing prevalence of the disease [2], along with evidence of poor outcomes in patients with gout [3, 4], has highlighted the need to improve gout management. To that end, four novel pharmacologic agents have been approved for the management of gout (i.e., hyperuricemia of gout or gout attacks) in the USA since 2009. With new drugs under development, particularly ones with unclear safety, it is imperative that subjects enrolled into trials are those who actually have the disease of interest before exposing them to study medications.

However, the conduct of such trials has historically been hampered by reliance on classification criteria dating from 1977 [5], which were not originally independently validated and focused primarily on identification of acute gout. Other published criteria have similar limitations [6, 7]. Numerous clinical trials, genome-wide association studies, and epidemiologic studies of gout have been undertaken that require accurate phenotyping to enable comparisons across studies, yet a standard, validated means of classifying individuals for such studies beyond these prior criteria were not available. While the gold standard for identifying gout is by documentation of the presence of monosodium urate (MSU) crystals in synovial fluid or tophus aspiration, this is often infeasible in the context of clinical research studies, especially as most such patients are typically recruited from primary care practices. Thus, a means of accurately identifying patients with gout without necessarily relying on MSU crystal identification would be useful to facilitate subject recruitment, particularly from primary care practices. Further, new imaging modalities that have aided our understanding of urate deposition, inflammation, and joint destruction had not been a part of the prior criteria. These were among the issues identified as the motivation to pursue development of new classification criteria for gout to advance the research agenda in gout in the modern era [8••], taking advantage of newer methodologies that could improve the accuracy of new criteria. In 2015, the American College of Rheumatology (ACR)-European League Against

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Rheumatism (EULAR) Gout Classification Criteria were published [9••, 10••], which reflected the culmination of an international collaborative effort to incorporate a data-driven process with state-of-the-art methodology to develop validated criteria to support these various gout research endeavors.

What Is the Purpose of Classification Criteria, and How Do They Differ from Diagnostic Criteria?

Before elaborating upon the rationale for developing new classification criteria, it is important to highlight that classification criteria are not intended to be used as diagnostic criteria in clinical practice. The primary intention of classification criteria is to provide researchers with a validated and standardized means of identifying subjects for enrollment into studies, thereby enabling creation of uniform cohorts, comparable across different studies and geographic regions. Thus, classification criteria generally only capture the key common features of the condition, not all possible and rare manifestations. They are usually unable, therefore, to identify all individuals with the disease of interest in the absence of a sensitive and feasible gold standard. In contrast, diagnostic criteria are used in routine clinical practice to guide the care of individual patients [11•, 12•] since clinicians must make the diagnosis in an individual even in the absence of common features or a gold standard.

Since classification criteria are designed for use in the research setting, including clinical trials of new drugs with little known safety profiles, they usually prioritize specificity over sensitivity. The primary motivation in a clinical trial is to enroll subjects who definitely have the disease to justify exposing them to the potential harms of a new therapy and to be able to accurately quantify benefit of therapy; an individual without the disease is unlikely to benefit from the therapy, while being unnecessarily put at risk of adverse events. Specificity becomes even more important as therapeutic complexity and risk of toxicity rises, including the use of biological drugs and pharmacological combinations. Sensitivity must also be optimized in classification criteria from a public health perspective to ensure that the public health burden of the disease can be accurately assessed.

In contrast, diagnostic criteria should ideally achieve both positive predictive value and negative predictive value of 100 % at different time-points and varying stages of disease to capture all patients that have the disease and exclude anyone not having the disease. Achieving these characteristics is challenging, especially for diseases that lack a gold-standard diagnosis definition. Performance characteristics of diagnostic criteria may be different in distinct geographic regions that differ in the prevalence of the disease in question and its differential diagnosis. These types of issues limit the ability to create uniform diagnostic criteria that can be used worldwide [11•, 12•].

Limitations of Previous Classification Criteria for Gout

Prior to the 2015 ACR-EULAR Gout Classification Criteria [9••, 10••], there existed three classification criteria for gout [5–7], and two other criteria developed for diagnostic purposes [13, 14].

The original three classification criteria relied on expert opinion [6, 7] or physician diagnosis [5] of gout, which creates issues of circularity. That is, the physician/investigator has inherent ideas about what constitutes gout, and by labeling a subject as having gout based on those elements, the criteria are biased toward those elements. Studies evaluating the performance of these older classification criteria in crystal-proven gout patients revealed limited sensitivity and specificity [15, 16]. The specificity for the New York and the 1977 American Rheumatism Association (ARA, now the ACR) criteria varies from 47 to 88 % depending on disease duration, while the sensitivity is 58–71 % in early disease (up to 2 years) and 88–92 % among patients with established disease when restricted to evaluation of the clinical items only [15]. Because both of these criteria consider MSU crystal identification as sufficient criteria to classify a subject as having gout, they naturally achieve 100 % sensitivity when tested in a cohort of crystal-proven gout patients. The Rome criteria include MSU crystal identification among the list of items, but not as sufficient feature for classification. The Rome criteria have a sensitivity ranging from 60 % (clinical items only, early disease) to 99 % (full criteria (including MSU positivity), established disease), with specificity of 86 and 64 %, respectively, among patients with early and established disease [15]. Another study evaluating the clinical items of the three criteria sets in a sample of 30 crystal-proven gout patients and 52 nongout subjects reported sensitivity ranging between 67 and 70 %, and specificity from 79 to 86 % [16]. Thus, each of the previously published criteria had suboptimal sensitivity (in the absence of MSU crystal identification) and specificity.

Of these three older classification criteria, only the 1977 ARA preliminary criteria for the classification of the acute arthritis of primary gout included imaging features, namely asymmetric swelling within a joint and subcortical cysts without erosions on conventional radiography. These radiographic changes are neither specific for gout nor common in the first years of disease [17], limiting their usefulness in classifying individuals earlier in the course of their disease. The prior criteria also included only limited comparator conditions in their development (Table 1). In summary, the prior published criteria's validity was limited by the gold standard used

Table 1 Previously published classification criteria for gout

	Rome 1963 [6]	New York 1966 [7]	ARA preliminary classification criteria for acute gout 1977 [5]
Items	1. Serum uric acid >7 mg/dL in men and >6 mg/dL in women	1. At least two attacks of painful joint swelling with complete resolution with 2 weeks	1. More than one attack of acute arthritis
	2. Presence of tophi	2. A history or observation of podagra	2. Maximum inflammation developed within 1 day
	3. MSU crystals in SF or tissue	3. Presence of tophi	3. Oligoarthritis attack
	4. History of attacks of painful joint swelling with abrupt onset and resolution within 2 weeks	4. Rapid response to colchicine treatment, defined as a major reduction in the objective signs of inflammation within 48 h	4. Redness observed over joints
			5. First MTP joint painful or swollen
			6. Unilateral first MTP joint attack
			7. Unilateral tarsal joint attack
			8. Tophus (suspected or proven)
			9. Hyperuricemia (more than 2 S.D. greater than the normal population average)
			10. Asymmetric swelling within a joint on X-ray
			11. Subcortical cysts without erosions on X-ray
			12. Complete termination of an attack
Case definition	Two or more of any criteria	Two or more of any criteria OR presence of MSU crystals in SF or on deposition	Six of 12 clinical criteria required OR presence of MSU crystals in SF or in tophus
Limitations of these criteria	Developed based on expert opinion		Physician diagnosis considered to be the gold standard. MSU crystal identification was not used to define cases during development process.
			Controls limited to patients with RA, acute calcium pyrophosphate crystal arthritis and acute septic arthritis—common mimickers such as OA, PsA, and reactive arthritis excluded.
			SF examination performed in only 51 % of gout patients and in 47 % of the controls. Of the gout patients that underwent synovial analysis, only 84 % had MSU crystals identified.
	Developed prior to availability of advanced imaging modalities.		

ARA American Rheumatism Association, *MSU* monosodium urate, *SF* synovial fluid, *MTP* metatarsophalangeal, *SD* standard deviations, *RA* rheumatoid arthritis, *OA* osteoarthritis, *PsA* psoriatic arthritis

(expert opinion/physician diagnosis), performance characteristics, and inclusion of limited imaging parameters (Table 1).

Impact on Understanding the Prevalence of Gout

From a public health perspective, accurate classification of gout is important for health care resource planning in the context of understanding prevalence and prevalence trends. From an epidemiologic perspective, accurate classification and phenotyping of gout provide valid insights into risk factors for disease, including identification of genetic risk factors. Gout is now recognized to be the most common inflammatory arthritis, especially in men, associated with high morbidity and mortality rates, with increasing prevalence in both males and females, regardless of socioeconomic status. The prevalence of gout has been reported to vary from 0.1 to approximately 10 %, with the greatest proportions identified among Taiwanese aboriginals and Maori [18]. In the USA, the prevalence of self-reported gout among adults (≥20 years old) is 3.9 % based on data from the National Health and Nutrition Examination Survey (NHANES) 2007–2008 [19], with this prevalence having increased from 2.9 % in the prior period (1988–1994) [20]. A study in the UK using data from primary care practices reported a 63.9 and a 29.6 % increase, respectively, in prevalence and incidence of gout from 1997 to 2012 [21]. Gout prevalence in New Zealand follows a similar trend, having increased from 2.9 % in 1992 [22] to 3.2 % in 2009 [23] among European descendants. The rise in prevalence among Maori males is more striking, with prevalence of 4.5 to 10 % between 1956 and 1984 [22] that increased to 13.9 % in 1992 [22] and to 18.4 % in 2011 [24].

These differences in prevalence between groups and across time must be interpreted in the context of findings of a systematic review with meta-regression on gout prevalence that identified a high level of heterogeneity among studies [25]. The authors concluded that the large variation in the prevalence data was explained by sex, continent on which the study had been performed, and the case definition of gout [25]. Thus, part of the difficulty in interpreting differences in prevalence across geographic regions, racial/ethnic groups, and time lies in the lack of a standardized means of identifying individuals with gout.

Increasing Research Efforts in Gout

The recent increase in the number of studies on gout highlights the need for a valid and standard means of ensuring comparability of study samples across studies. The number of articles indexed in PubMed about gout published between 2006 and 2015 was 2685, which is 2.3 times that published in the period between 1996 and 2005.

A number of factors have contributed to the renewed interest in gout from a research perspective. One reason as outlined above has been the recognized rise in gout prevalence over the past decades and the poor outcomes experienced by patients with gout [2–4, 26–32]. A second motivation for research in the field was advances in the understanding of disease pathophysiology. The discovery of the fundamental role of innate immunity in gout flares and the complexity of the inflammatory process triggered by MSU crystals have given gout a more prominent position than it had previously occupied in comparison with other inflammatory arthritis conditions [33]. Finally, as had happened in the field of rheumatoid arthritis after decades of relatively little advancement, the development of new drugs for gout has greatly fostered research in this disease. Urate-lowering therapy had been limited to allopurinol, probenecid, sulfinpyrazone, and benzbromarone since the 1960s. Three new urate-lowering medications were approved since 2009—febuxostat, pegloticase, and lesinurad—and other additional compounds are currently being developed [34]. Similar advances have occurred regarding treatment and prevention of gout attacks, primarily guided by the better understanding of cytokines involved. While the previously available agents had for a long time been nonsteroidal anti-inflammatory drugs, steroids, and generic colchicine, Colcrys was FDA-approved for gout attack management in 2009, and there are currently three interleukin-1 antagonists not yet approved as therapeutic options for gout attacks in the USA; canakinumab has been approved by the EMA [35]. Just as for epidemiologic studies of prevalence and burden of disease, standardized and validated criteria are important for enabling accurate understanding of the study samples and general comparisons of efficacy across trials.

Advances in Gout Imaging

Ultrasound (US), dual-energy computed tomography (DECT), and magnetic resonance imaging are among the current imaging modalities that can identify urate deposition, structural joint damage, and joint inflammation in gout, with a potential role in the diagnosis and follow-up of patients [36]. DECT is particularly attractive as it can differentiate calcium from urate crystal deposition when deposits are of sufficient size [37]. Because these imaging modalities are more sensitive than radiography, which only permits visualization of later-stage bone changes, these newer modalities offer opportunity to potentially identify gout earlier in the course of disease. In the research setting, these modalities have been useful in clarifying anatomical and pathophysiological features, such as the relation of tophi and bone erosions, and the presence of tissue inflammation around even small deposits of urate. Such imaging modalities are also being explored for use in defining outcome measures in clinical trials, particularly for evaluating tophus response to urate-lowering treatment [38].

A recent systematic literature review identified 11 studies that have evaluated DECT and US in the context of MSU crystal identification as the gold standard [39•]. Only three features had been examined in more than one study: the double contour sign on US, tophus on US, and MSU crystal deposition on DECT [39•]. The sensitivity and specificity of these features were, respectively, 83 % (95 % CI 72–91) and 76 % (95 % CI 68–83) for the US double contour sign, 65 % (95 % CI 34–87) and 80 % (95 % CI 38–96) for tophus on US, and 87 % (95 % CI 79–93) and 84 % (95 % CI 75–90) for DECT. These results reinforced the potential role for these imaging features in gout classification [39•].

MSU Crystals as the Gold Standard in Gout

Few diseases in rheumatology have a gold standard definition for diagnosis. The identification of MSU crystals in synovial fluid or tissue is the gold standard for the diagnosis of gout. Unfortunately, arthrocentesis and synovial analysis are not commonly performed, especially in the primary care setting [40, 41], where most gout patients are seen. In addition, aspiration of small joints and/or accurate use of a polarizing microscope may be difficult for nonexperts. If all research studies of gout required the identification of MSU crystals as inclusion criteria, the number of eligible patients would be significantly reduced and the clinical pattern of included subjects would be biased toward more involvement of large joints, and in many instances, large epidemiological studies would be infeasible. For example, in the Health Professionals Follow-Up Study, which is arguably one of the largest studies on risk factors for gout, only 7 % of the gout subjects were crystal-proven [42].

The Need for New Gout Classification Criteria

Thus, with the identified limitations in prior existing criteria, a burgeoning interest in gout research necessitating a reexamination of how subjects are identified for inclusion in studies, advances in imaging modalities that may be more sensitive in identifying gout, and the difficulty in identifying gout through joint or tophus aspiration with MSU crystal identification, particularly in primary care where the majority of patients with gout are managed, a clear need for developing new classification criteria for gout was recognized.

In recognition of these needs, in 2012, ACR and EULAR formally supported an international collaborative effort to develop new criteria.

2015 ACR-EULAR Gout Classification Criteria

The development of the 2015 ACR-EULAR Gout Classification Criteria [9••, 10••] encompassed a multistep and data-driven process with the participation of an international group of investigators with an interest and expertise in gout comprising rheumatologists, primary care physicians, and methodologists, together with the support of the ACR and EULAR. The process involved three main phases: (1) item generation, which comprised a Delphi exercise, systematic literature review of advanced imaging in gout (discussed above), and a data-driven identification of elements most strongly associated with crystal-proven gout; (2) selection and weighting of items for the new criteria, which comprised a consensus meeting to develop domains and categories, followed by a multicriterion decision analytic approach to derive the weights for each category; (3) final criteria refinement, with definition of the criteria's threshold for classifying as gout, and validating the final criteria in an independent dataset.

Item Generation

The first step in the item generation phase was a Delphi exercise with gout patients and gout experts to identify features potentially able to discriminate between gout and nongout [43•]. The systematic literature review of advanced imaging modalities discussed above was also part of this preparatory work [39•].

These identified features, together with the elements of the previously published criteria, comprised the content evaluated in the next step, an international cohort study (Study for Updated Gout Classification Criteria (SUGAR)) (983 subjects, in total) that was intended to provide a data-driven evaluation of the strength of association of the various identified features with MSU crystal-proven gout versus MSU-negative mimickers of gout [44•]. The inclusion criteria were joint swelling or a subcutaneous nodule within the previous 2 weeks that could conceivably be due to gout, with aspiration of the symptomatic joint or nodule, followed by crystal examination performed by a certified observer [45]. Subjects were categorized by the result of the crystal analysis as MSU-positive or MSU-negative. From this sample, a random two-thirds of the study subjects composed the derivation data set, whereas the remaining one third was kept for the validation phase of the final criteria without use in any other analyses.

From the development dataset, the SUGAR study identified ten key features for discrimination between MSU-positive gout and other MSU-negative conditions: (1) joint erythema, (2) at least one episode involved difficulty walking, (3) time to maximal pain less than 24 h, (4) resolution by 2 weeks, (5) tophus, (6) first metatarsophalangeal joint ever involved, (7) location of currently tender joints, (8) serum urate level >6 mg/dL (0.36 mmol/L), (9) US double contour sign, and (10) radiographic erosion or cyst.

Selection and Weighting of Items

The second phase of the criteria development process began with an exercise aimed at addressing potential limitations of phase 1. Selection bias was anticipated in the SUGAR study since all subjects were required to undergo arthrocentesis or aspiration of a nodule; this could potentially bias the study sample toward subjects with more severe disease, larger joints involvement, or tophus. Selection bias was also possible related to the fact that most subjects were recruited from rheumatology clinics where more severe cases of gout may be managed, rather than primary care settings, where most gout patients are seen. Thus, the spectrum of disease severity was extended in phase 2 through use of paper patient cases. The data from phase 1, in addition to the paper cases, were used as the basis to identify the relevant domains and categories within the domains important in distinguishing gout from other conditions that could be mimickers of gout.

Once the domains and categories were identified, a multicriterion decision analytic approach (i.e., conjoint analysis) was used to derive the weights for each category. Specifically, we conducted a series of forced-choice experiments between two hypothetical scenarios, where two attributes are compared at a time, assuming that the scenarios were otherwise equal with regard to all other features and only differ in the two attributes being considered [46•]. For example, in scenario A (Fig. 1), attribute 1, joint erythema, conveys a "higher probability of gout" than in scenario B which does not have joint erythema, but attribute 2 (fast time of onset to maximal pain) in scenario B conveys a higher probability of gout than in scenario A (slower time to onset of maximal pain). One must decide which of these two scenarios is more likely to have gout, considering all other parameters to be equal. In this way, each attribute is implicitly judged and weighted. The series of forced-choice experiments continue until all relevant pairwise comparisons are evaluated [46•].

Even though conjoint analysis has been used for more than 40 years, mostly in marketing studies, its use in rheumatology is much more recent, though still not well-known among physicians [47•, 48, 49]. The methodology builds upon the assumption that different features of the same product or concept—for example, a disease—do not have the same relevance and therefore should not have equal weights. In rheumatology, one of the first uses of conjoint analysis was in the development of the 2010 Rheumatoid Arthritis Classification Criteria [48]. In the final criteria, the domain of joint involvement, for example, encompasses five levels, from "one large joint," which is given a score (weight) of zero, to ">10 joints (including at least 1 small joint)," which is scored as five. Of note, by the methodology used for that endeavor, the lowest category in each domain is weighted as zero. From a clinical perspective, it is easily understandable that different patterns of joint involvement are associated with different probabilities of rheumatoid arthritis, and not necessarily in a simple incremental manner. Further, it is readily appreciated that presence of rheumatoid factor does not convey the same probability as presence of an elevated erythrocyte sedimentation rate. Accurately weighting these, though, is complicated and cognitively challenging when one needs to simultaneously consider all of the other elements. The forced-choice experiments are less cognitively challenging in that regard, since they only require pairwise comparisons, which contributes, in part, to more accurate results than using rating scales or ranking. Thus, forced-choice experiments offer an expedient means of obtaining weights for these cognitively challenging comparative considerations.

In contrast, the majority of previous classification criteria have typically been scored through simple summing of equally weighted items, often in the form of counting the number of elements present. For instance, the 1977 ARA preliminary criteria for gout would classify an individual as gout if 6 of 12 clinical criteria were present, regardless of which specific items, implicitly weighting each item equally [5]. In such case, a tophus would contribute the same probability of gout as unilateral tarsal joint attack, for example. With this type of approach, accuracy and performance characteristics (i.e., sensitivity and specificity) are likely to be suboptimal.

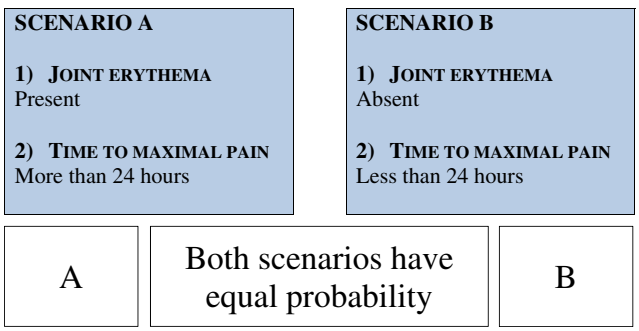

Fig. 1 A hypothetical example of a forced-choice experiment used to inform the weights of each category within the domains

Final Criteria

With domains and categories defined and respective weights assigned, the threshold that had the best performance characteristics to classify a subject as having gout was identified in a data-driven manner in two ways. First, the cutoff score that maximized efficiency, i.e., the sum of sensitivity and specificity, in the SUGAR derivation cohort was identified in terms of differentiating MSU-positive subjects from those that were MSU-negative. Second, in a separate exercise, the expert panel indicated whether they would enroll each paper patient into a phase 3 trial. The threshold at which the panel had high enough confidence to enroll into a phase 3 trial was consistent with the data-driven threshold identified. The final classification criteria's possible scores range from −6 to 23, with the

Table 2 The ACR/EULAR Gout Classification Criteria

	Categories	Score
Step 1: Entry criterion (only apply criteria below to those meeting this entry criterion)	At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa	
Step 2: Sufficient criterion (if met, can classify as gout without applying criteria below)	Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus	
Step 3: Criteria (to be used if sufficient criterion not met)		
Clinical		
Pattern of joint/bursa involvement during symptomatic episode(s) ever[a]	Ankle *or* mid-foot (as part of monoarticular or oligoarticular episode without involvement of the first metatarsophalangeal joint)	1
	Involvement of the first metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
Characteristics of symptomatic episode(s) ever		
• Erythema overlying affected joint (patient-reported or physician-observed)	One characteristic	1
• Can't bear touch or pressure to affected joint	Two characteristics	2
• Great difficulty with walking or inability to use affected joint	Three characteristics	3
Time course of episode(s) ever		
Presence (ever) of ≥2, irrespective of anti-inflammatory treatment:		
• Time to maximal pain <24 hours	One typical episode	1
• Resolution of symptoms in ≤14 days	Recurrent typical episodes	2
• Complete resolution (to baseline level) between symptomatic episodes		
Clinical evidence of tophus		
Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)	Present	4
Laboratory		
Serum urate: Measured by uricase method.		
Ideally should be scored at a time when the patient was not receiving urate-lowering treatment and it was >4 weeks from the start of an episode (i.e., during intercritical period); if practicable, retest under those conditions. The highest value irrespective of timing should be scored.	<4 mg/dL (<0.24 mmol/L)[b]	–4
	6– <8 mg/dL (0.36– <0.48 mmol/L)	2
	8– <10 mg/dL (0.48– <0.60 mmol/L)	3
	≥10 mg/dL (≥0.60 mmol/L)	4
Synovial fluid analysis of a symptomatic (ever) joint or bursa (should be assessed by a trained observer)[c]	MSU negative	–2
Imaging		
Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: ultrasound evidence of double-contour sign[d] or DECT demonstrating urate deposition[e]	Present (either modality)	4
Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrates at least 1 erosion[f]	Present	4

A web-based calculator can be accessed at: http://goutclassificationcalculator.auckland.ac.nz, and through the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) web sites [9••, 10••]. Reprinted by permission of *Arthritis & Rheumatology*/John Wiley and Sons and *Annals of the Rheumatic Diseases*/BMJ.

[a] Symptomatic episodes are periods of symptoms that include any swelling, pain, and/or tenderness in a peripheral joint or bursa

[b] If serum urate level is <4 mg/dL (<0.24 mmol/liter), subtract 4 points; if serum urate level is ≥4–<6 mg/dL (≥0.24–<0.36 mmol/L), score this item as 0

[c] If polarizing microscopy of synovial fluid from a symptomatic (ever) joint or bursa by a trained examiner fails to show monosodium urate monohydrate (MSU) crystals, subtract 2 points. If synovial fluid was not assessed, score this item as 0. If imaging is not available, score these items as 0

[d] Hyperechoic irregular enhancement over the surface of the hyaline cartilage that is independent of the insonation angle of the ultrasound beam (note: false-positive double-contour sign [artifact] may appear at the cartilage surface but should disappear with a change in the insonation angle of the probe)

[e] Presence of color-coded urate at articular or periarticular sites. Images should be acquired using a dual-energy computed tomography (DECT) scanner, with data acquired at 80 and 140 kV and analyzed using gout-specific software with a two-material decomposition algorithm that color-codes urate. A positive scan is defined as the presence of color-coded urate at articular or periarticular sites. Nailbed, submillimeter, skin, motion, beam hardening, and vascular artifacts should not be interpreted as DECT evidence of urate deposition

[f] Erosion is defined as a cortical break with sclerotic margin and overhanging edge, excluding distal interphalangeal joints and gull wing appearance

threshold to classify gout being ≥8 (Table 2) [9••, 10••]. These new criteria were tested in the validation cohort of SUGAR, with a sensitivity of 92 % and specificity of 89 %, which represents an accuracy of 95 %. When limited to only clinical features without synovial fluid analysis or imaging, the sensitivity and specificity were 85 and 78 %, respectively, maintaining a satisfactory accuracy of 89 %. These performance characteristics were an improvement over prior published criteria [9••, 10••].

The Role of Classification Criteria as an Educational Tool

While it is important to highlight that classification criteria should not be used as diagnostic criteria and should have no or little impact on clinical practice, there is a potential clinical role for classification criteria as an educational means of highlighting key features of a disease. It is recognized that nonspecialists and new learners within a medical specialty may commonly use classification criteria as an initial tool to understand common or key features of disease [50]. In this regard, the 2015 ACR/EULAR classification criteria for gout can be useful to highlight that joint patterns of involvement other than the first metatarsophalangeal are possible in gout and gout should therefore be considered in the differential diagnosis. The criteria also highlight the gold standard nature of MSU crystal identification as a sufficient criterion. The utility of laboratory tests, particularly the absence of hyperuricemia and of MSU crystal identification in synovial fluid, emphasizes these as important factors that reduce the likelihood of gout. In particular, the "dose-dependent" effect of serum urate is an important insight, whereby higher serum urate levels increase the likelihood of gout, while lower serum urate diminishes the likelihood of gout, and very low levels can help to rule out the disease. Although imaging is not needed or sufficient to ascertain the diagnosis of gout, some typical features in conventional radiography, US, or DECT can be helpful in certain cases.

Conclusions

The 2015 ACR-EULAR Gout Classification Criteria [9••, 10••] will aid the advancement of the research agenda in gout by providing researchers with a validated, standardized means of identifying a relatively homogeneous group of well-characterized patients with gout for inclusion in clinical studies. These criteria maintain high-performance characteristics even when synovial fluid analysis and imaging data are unavailable, increasing their feasibility for use in large-scale epidemiologic studies. It is anticipated that the 2015 ACR-EULAR Gout Classification Criteria [9••, 10••] will facilitate ongoing research endeavors in gout worldwide.

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Compliance with Ethical Standards

Conflicts of Interest ABVS and WJT declare that they have no conflicts of interest. TN reports that she was the ACR-PI of the 2015 ACR-EULAR Gout Classification Criteria report.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and were in compliance with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
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