# Patient-reported Outcomes in Chronic Gout: A Report from OMERACT 10

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***ABSTRACT.*** ***Objective***. To summarize the endorsement of measures of patient-reported outcome (PRO) domains in chronic gout at the 2010 Outcome Measures in Rheumatology Meeting (OMERACT 10).

***Methods.*** During the OMERACT 10 gout workshop, validation data were presented for key PRO domains including pain [pain by visual analog scale (VAS)], patient global (patient global VAS), activity limitation [Health Assessment Questionnaire-Disability Index (HAQ-DI)], and a disease-specific measure, the Gout Assessment Questionnaire version 2.0 (GAQ v2.0). Data were presented on all 3 aspects of the OMERACT filters of truth, discrimination, and feasibility. One PRO, health-related quality of life measurement with the Medical Outcomes Study Short-form 36 (SF-36), was previously endorsed at OMERACT 9.

***Results.*** One measure for each of the 3 PRO of pain, patient global, and activity limitation was endorsed by > 70% of the OMERACT delegates to have appropriate validation data. Specifically, pain measurement by VAS was endorsed by 85%, patient global assessment by VAS by 73%, and activity limitation by HAQ-DI by 71%. GAQ v2.0 received 30% vote and was not endorsed due to several concerns including low internal consistency and lack of familiarity with the measure. More validation studies are needed for this measure.

***Conclusion.*** With the endorsement of one measure each for pain, patient global, SF-36, and activity limitation, all 4 PRO for chronic gout have been endorsed. Future validation studies are needed for the disease-specific measure, GAQ v2.0. Validation for PRO for acute gout will be the focus of the next validation exercise for the OMERACT gout group. (J Rheumatol 2011;38:1452–7; doi:10.3899/jrheum.110271)

*Key Indexing Terms:*
PATIENT-REPORTED OUTCOMES CHRONIC GOUT VALIDATION PAIN
PATIENT GLOBAL FUNCTIONAL LIMITATION

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Patient-reported outcomes (PRO) are important to patients with musculoskeletal conditions just as they are to the assessment of the impact of disease and treatment of other chronic conditions. Various regulatory agencies including the US Food and Drug Administration (FDA)[1] recognize PRO as important outcomes in the assessment of new drugs; several new biologics approved for treatment of rheumatoid arthritis (RA) have an approved PRO label claim. Many initiatives such as the Patient-Reported Outcomes Measurement Information System (PROMIS) have helped to focus on PRO as important indicators of health-related quality of life (HRQOL) in chronic diseases and outcomes that matter to the patient[2]. This is a paradigm shift from the longstanding emphasis on end-organ damage or failure (renal failure, myocardial infarction, stroke, etc.) and death as relevant outcomes of chronic diseases.

Gout is a potentially progressive and debilitating chronic inflammatory arthritis associated with pain, disability, reduction in HRQOL and ultimately in productivity, as well as morbidity[3,4,5,6,7,8,9]. At the OMERACT 9 Meeting in 2008, outcome domains were validated for chronic gout[10,11] and included an inner circle of mandatory domains with validated instruments for their measurement and an outer circle of desirable domains. Patients were integral to this discussion, as in other OMERACT activities. The inner circle included these PRO: pain, patient global, HRQOL by Medical Outcomes Study Short-form Survey 36 (SF-36), and activity limitation (Figure 1). The efforts of the OMERACT gout group over the last 2 years have focused on validation of remaining PRO domains in patients with chronic gout. This article summarizes progress in validation of measures for these PRO domains: pain by visual analog scale (VAS), patient global by VAS, Health Assessment Questionnaire (measuring activity limitations), and Gout Assessment Questionnaire (GAQ), a disease-specific measure of activity limitation and HRQOL. Further, we summarize data presented at the gout workshop at OMERACT 10 in Borneo, Malaysia, and describe the OMERACT endorsement of these measures specifying truth, discrimination, and feasibility for each measure. The detailed validation analyses of the PRO are the focus of separate articles submitted for publication, and are beyond the scope of this report.

## Pain

Pain is a cardinal symptom of acute gout flare. Pain is an important feature of chronic gout as it is for other inflammatory arthritides including RA and spondyloarthropathies. The importance of pain as a feature of chronic gout is exemplified by its inclusion in the inner circle for the domains (Figure 1).

Pain measurement by VAS was endorsed by 85% of voters as meeting the OMERACT filters of truth, discrimination, and feasibility based on data presented (Table 1). Data presented in preparation for discussion and voting came from 2 replicate randomized controlled trials (RCT) of pegloticase versus placebo[12] that enrolled 225 patients with tophaceous gout, across 56 centers. PRO data from these 2 RCT were combined (as per FDA and company's agreement; note that the primary endpoint, as opposed to clinical endpoints, was separately analyzed) since the trials had the same methodology, design, duration (6 months), treatment interventions, and outcomes. Data presented were from baseline and end of the study visits. VAS pain has been used extensively, and therefore, has face and content validity; the specific question used in the studies is shown in Figure 2. Divergent validity was examined by comparing VAS pain scores across varying baseline tender and swollen joint counts, and SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) score quartiles. For discrimination, VAS pain scores were compared between the treatment arms and placebo, and estimates of clinically important differences were presented. As a single question, VAS pain was regarded as feasible for the clinical trial setting.

Although not formally voted upon, a separate analysis was also presented for SF-36 bodily pain domain as a measure of pain. The SF-36 instrument as a measure of HRQOL has been validated in gout and endorsed at OMERACT 9. Analyses were derived from the above RCT of pegloticase[12] and 2 RCT with febuxostat[13,14]. Assessment of the "truth" component of the OMERACT filter for this measure included an assessment of divergent validity by baseline number of tender and swollen joint counts, baseline disease duration, and presence of tophi. Discrimination included comparison of treatment arms.

During the breakouts, several important aspects were discussed. Discussants agreed with using the SF-36 bodily pain domain as a measure of pain severity in chronic gout. Discussants agreed that a numeric rating scale (NRS) could be substituted for the VAS. Discussants also commented that pain could be influenced by acute flares, as well as by other chronic pain conditions such as concomitant osteoarthritis and/or back pain or fibromyalgia.

## Patient Global Assessment Scale

Patient global assessment of disease scales are commonly used in RCT and longitudinal observational studies (LOS) and often used as a gold standard to determine clinically meaningful changes. Validation data were derived from the 2 above

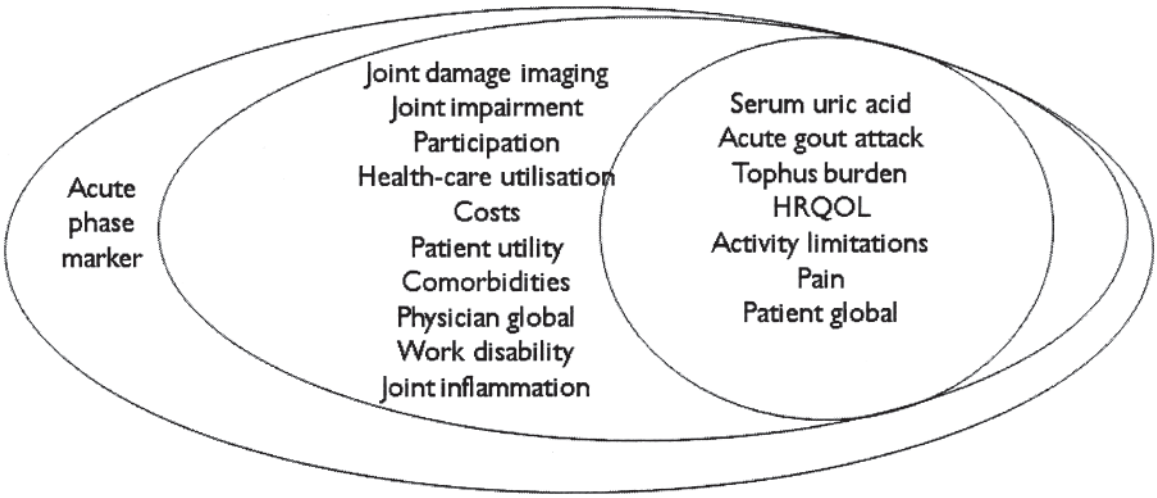


*Figure 1.* Outcome measures in chronic gout. Key domains for chronic gout as endorsed in 2008 at OMERACT 9. HRQOL: health-related quality of life.

*Table 1.* OMERACT voting results for the patient-reported outcome measures for chronic gout. A voting result for validation of 70% or higher is considered endorsement for a given measure.

| Domain | Measure | OMERACT Voting | | Comments During Breakouts |
|---|---|---|---|---|
| | | Counting All Votes (%) | Excluding "Don't know" Responses (%) | |
| Pain | VAS pain | 62/73 (85) | 62/67 (91) | A numeric rating scale could substitute for VAS |
| | SF-36 pain | — (71)[a] | — | SF-36 endorsed during previous OMERACT; discussants comfortable using SF-36 pain as substitute for VAS |
| Patient Global | VAS | 55/75 (73) | 55/62 (89) | |
| Activity Limitation | HAQ-DI | 54/76 (71) | 54/59 (91) | |
| Disease specific measure | GAQ v2.0[b] | 22/74 (30) | 22/40 (56) | Lack of familiarity with measure; concerns regarding validation |

[a] Endorsement for the entire SF-36 at OMERACT 9 (reference); [b] Only the Gout Concern Overall Scale and Unmet Need Scale were evaluated. SF-36: Medical Outcomes Study Short-Form 36; HAQ-DI: Health Assessment Questionnaire Disability Index; GAQ v2.0: Gout Assessment Questionnaire, version 2.0; VAS: visual analog scale.

pegloticase RCT[12] and were similar to those presented for pain VAS (Table 2). Patient global met OMERACT filters of truth, discrimination, and feasibility and was endorsed by 73% of voters (Table 1).

**Activity Limitations**

Chronic gout is associated with chronic pain and inflammation, joint deformities and/or joint destruction, and deposition of urate as tophi in joints and subcutaneous tissues. Each of these can result in activity limitations in patients with chronic gout. These can be measured by general instruments such as Katz activities of daily living (ADL)[15]. Another commonly used instrument in rheumatic conditions is the Health Assessment Questionnaire (HAQ)[16]. The disability index of HAQ, HAQ-DI, has been used commonly in patients with RA and other rheumatic conditions[17].

Data regarding HAQ-DI were derived from the pegloticase RCT[12] and a longitudinal observational study[18]. In the observational study, HAQ-DI scores were significantly higher in subjects with any tender and/or swollen joints (vs none) or presence versus absence of tophi, and were significantly different between patients who improved versus those with no change or deterioration[18]. HAQ-DI was also shown to fit a Rasch measurement model in gout patients and to correlate in expected ways with other measures of physical performance[19]. HAQ-DI was felt to meet the OMERACT filters of truth, discrimination, and feasibility with 71% of voters endorsing the measure.

**VAS Pain**: How much pain have you had because of your illness in the past week

No pain (0)_____Severe pain (100)

**Patient Global**: Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line

Very Well (0)_____Very Poor (100)

*Figure 2*. Measures for pain and patient global assessment used in 2 RCT of pegloticase[12].

*Table 2.* Validation data presented for patient reported outcomes in chronic gout.

| | Truth | | | | Discrimination | | Feasibility |
|---|---|---|---|---|---|---|---|
| | Face Validity | Content Validity | Convergent/ Divergent | Internal Consistency | Between Treatments | Sensitivity To Change | |
| VAS pain | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| No. RCT | n/a | n/a | 2 | 2 | 2 | 2 | 2 |
| SF-36 pain | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| No. RCT | n/a | n/a | 4 | 4 | 4 | 4 | 4 |
| Patient global | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| No. RCT | n/a | n/a | 2 | 2 | 2 | 2 | 2 |
| HAQ-DI | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| No. studies | n/a | n/a | 2 | 2 | 2 | 2 | 2 |
| GAQ v2.0 | ✓ | ✓ | ? [a] | ? [b] | Not assessed | ✓ | ?[c] |
| No. studies | n/a | n/a | 1 | 1 | 0 | 1 | 2 |

[a]Correlations with SF-36 physical and mental component summary scores were low, raising issues regarding convergent validity;
[b]Low for Unmet Gout Need subscale, but high for Gout Concern Overall and other subscales of the Gout Impact Section (GIS) of GAQ v2.0;
[c] Feasibility has not been tested in research or clinical use settings. It has been self-administered by patients in one study, but the time to completion is 15-20 min.
VAS: visual analog scale; SF-36: Medical Outcome Study Short Form Survey 36; RCT: randomized controlled trials; HAQ-DI: Health Assessment Questionnaire Disability Index; GAQ v2.0: Gout Assessment Questionnaire version 2.0.

**Disease-specific Measure: GAQ v2.0**

Recently, a disease-specific instrument to measure HRQOL, impact of gout during acute attacks, unmet patient needs, and medication side effects and concerns has been developed[20]. A revised GAQ v2.0 was redeveloped following patient focus groups to assess various aspects of gout considered important to them.

The initial validation study of GAQ v2.0 was a 3-center cross-sectional study of 300 gout patients performed in the US from 2006 to 2008, focusing on the Gout Impact Section (GIS; Table 3)[21]. GAQ v2.0 was shown to have good face and content validity. Internal consistency for the Gout Concern Overall scale was good, with unadjusted Cronbach's alpha of 0.88 and adjusted Cronbach's alpha 0.94. Lower internal consistency was noted for 2 subscales: Medication Side Effects (0.60 and 0.86, respectively) and Unmet Gout Need (0.65 and 0.86, respectively)[17], and 0.35 in the RCT[22]. Test-retest reliability for the Gout Overall Concern subscale was 0.77, and for Unmet Treatment Need 0.76[21]. Construct validity showed correlation coefficients of –0.16 for Gout Concern Overall with PCS and –0.28 with MCS; for the Unmet Gout Treatment Need, respective correlation coefficients were –0.15 and –0.24[21]. The poor correlation with generic HRQOL instruments raised concerns regarding construct validity (truth). In an unpublished study, Gout Concern Overall showed sensitivity to change, with change scores for "markedly improved" much higher than for those who reported lesser or no change on a global scale[22]. Validation data for the Gout Impact Section (Gout Concern Overall, Unmet Gout Treatment Need) of GAQ v2.0 was thought to be acceptable by 30% of voters, thus indicating that GAQ v2.0 was not yet endorsed as a validated measure in gout.

Breakout session discussions revealed several questions and problems regarding GAQ v2.0:

1. Lack of familiarity with the questionnaire — most people had not heard of it and the majority had not seen the questionnaire.
2. What does it measure? Discussants were not sure which domains it measured — activity limitations, disability, HRQOL, acute versus chronic gout impact, need, adverse events? They found the structure of the GAQ confusing — and considered only the Gout Impact Section (GIS) relevant.
3. Issues with internal consistency — Discussants expressed concerns regarding the internal consistency and construct validity of the Unmet Gout Treatment Need subscale, but felt comfortable with the Gout Concern Overall subscale.

**Research Agenda**

Several items are proposed for the research agenda related to PRO in gout. Pain, patient global, HRQOL, and activity limitations assessed by HAQ-DI or similar instruments are considered validated in chronic gout, and should be validated in acute gout — a focus for the next OMERACT. Several questions of the GAQ v2.0 make it a good subject for future research and validation. Other important suggestions from breakout groups include the following:

1. Items should be framed in relation to acute versus chronic gout, and functional limitation and other items should be framed specifically for gout.
2. The PROMIS network should be explored for additional measures of PRO.
3. Minimum clinically important differences should be anchored by perceived change scores rather than the change in disease status scores.

*Table 3.* Gout Concern Overall and Gout Unmet Treatment Need subscales of the Gout Assessment Questionnaire v2.0. From J Rheumatology 2008;35:2406–14; copyright 2008 Takeda Global Research and Development Inc., adapted with permission.

Please answer every question. Read every question carefully and choose the best answer for you.

About How Gout Affects Your Daily Life Overall

1. Please indicate how much you agree or disagree with each of the statements below. (Mark one answer for each statement.)

| | Strongly Agree | Agree | Not Certain | Disagree | Strongly Disagree |
|---|---|---|---|---|---|
| a. I am worried that I will have a gout attack within the next year. | | | | | |
| b. I am afraid that my gout will get worse over time. | | | | | |
| c. I feel anxious that my gout will interfere with my future activities. | | | | | |
| d. I worry that I will not be able to continue to enjoy my leisure activities as a result of my gout. | | | | | |
| e. I am bothered by side effects from my gout medications. | | | | | |
| f. I am mad or angry when I experience a gout attack. | | | | | |
| g. It is difficult to plan ahead for events or activities because I may have a gout attack. | | | | | |
| h. I feel depressed when I experience a gout attack. | | | | | |
| i. My current medications are effective for treating a gout attack when I have one. | | | | | |
| j. I miss planned or important activities when I have a gout attack. | | | | | |
| k. I worry about long term effects of gout medications. | | | | | |
| l. My current medications do not work well to prevent gout attacks from happening. | | | | | |
| m. I have control over my gout. | | | | | |

Scales and items: Gout Concern Overall (4 items, 1 a-d); Unmet Gout Treatment Need (3 items, l i, l, m).

4. Further measurement of intermittent versus persistent pain, as well as impact of pain, should be considered.
5. Other PRO, such as fatigue, sleep, and social/work participation, should be explored to assess the impact of chronic as well as acute gout on the entire range of PRO.
6. In patients with chronic gout, distinction of PRO obtained during an acute flare versus between flares should be noted.

## Summary and Conclusions

Of the PRO, HRQOL measurement with SF-36 previously met the OMERACT filters and was endorsed at OMERACT 9. Based on data from 5 RCT and 2 longterm observational studies, PRO measures that met the OMERACT filters of truth, discrimination, and feasibility included the following: pain and patient global assessments by VAS and activity limitations by HAQ-DI. Additionally, most voters agreed that NRS could substitute for the VAS pain scale to allow data collection over the telephone, using personal digital assistants, and mailed surveys. The disease-specific composite measure, GAQ v2.0, did not meet the OMERACT filters; more research is required for its validation. With the endorsements obtained at OMERACT 9 and OMERACT 10, the gout working group has made significant advances. All 4 PRO domains included in the inner circle of chronic gout outcomes now have at least one validated outcome measure that both meets the OMERACT filters and has been endorsed by OMERACT. These PRO measures should be used in both RCT and LOS to assess the impact of disease and treatment interventions for gout. Nevertheless, this endorsement should not be interpreted as implying that additional measures of these domains should not be considered. However, any additional measures need validation data and endorsement. An important item on the research agenda for the PRO subgroup of the gout group includes the examination of PRO measures in acute gout.

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