

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmjjournals.org/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Flare Frequency, Health Care Resource Utilization, and Costs Among Patients with Gout in a Managed Care Setting: A Retrospective Medical Claims-Based Analysis
<b>AUTHORS</b>	Jackson, Robert; Shiozawa, Aki; Buysman, Erin; Altan, Aylin; Korrer, Stephanie; Choi, Hyon

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Albert I Wertheimer Temple University Philadelphia, USA
<b>REVIEW RETURNED</b>	01-Jan-2015

<b>GENERAL COMMENTS</b>	<p>This is a very well conceptualized, organized and written manuscript. This reviewer asks only two questions: It was not clear how the wealth and ethnicity information had been gathered and whether collection of this information was consented by gout patients.</p> <p>Also, how do you deal with misdiagnoses so common by GP physicians and other non-rheumatologists?</p> <p>One other overall comment will be thought by any future reader - Would not everyone expect that more flares equals greater expense? I would assume that more MIs means greater expense. Was there some literature that questioned this? Otherwise, while the study and report are very well done, one must ask if there is/was a need for the study and what its contribution to the literature might be.</p>
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<b>REVIEWER</b>	Karen Rascati University of Texas, Austin TX, USA
<b>REVIEW RETURNED</b>	23-Jan-2015

<b>GENERAL COMMENTS</b>	I do not know why the authors collapsed zero flares and one flare. I can understand 3+ collapse, but if they want to make the point that avoiding flares is cost-effective - they need to break out the zeros and ones. I am willing to re-look at it if they do this.
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a very well conceptualized, organized and written manuscript. This reviewer asks only two questions: It was not clear how the wealth and ethnicity information had been gathered and whether collection of this information was consented by gout patients.

We have described the source of the wealth and ethnicity information in the Methods section: "Patient ethnicity and net worth information were captured from linked socioeconomic status data. These data were generated by a combination of self-report, modeling, census data, and a variety of other individual-level and population-level data sources."

Also, how do you deal with misdiagnoses so common by GP physicians and other non-rheumatologists?

We agree that this is a limitation associated with use of medical claims data, and we have addressed this limitation in the Discussion section: "Claims data may be subject to possible coding errors, and the presence of a medical claim may not always indicate disease (e.g., it may be included as rule-out criteria). The claims-based algorithms used in this study to identify gout patients were not validated with a medical chart review, and it is possible that some patients selected for study inclusion did not have gout. However, the algorithms required presence of either multiple gout diagnoses or presence of a gout diagnosis and a medication, and we expect this approach increased the specificity of patient selection. Also, in a sensitivity analysis where more restrictive criteria were used for patient selection (use of patient identification algorithms 1 and 2, but not 3), we observed similar trends when comparing costs among cohorts (data not shown)."

One other overall comment will be thought by any future reader - Would not everyone expect that more flares equals greater expense? I would assume that more MIs means greater expense. Was there some literature that questioned this? Otherwise, while the study and report are very well done, one must ask if there is/was a need for the study and what its contribution to the literature might be.

We agree with the reviewer that it would be assumed that patients with frequent flares would have higher expenses. However, our study sought to provide more insight into this question by actually quantifying the expenses and comparing them among different cohorts, and we have explained this further in the Discussion section. We also agree that others have investigated the relationship between flare frequency and costs among patients with gout. In particular, we reference studies by Lynch et al. and Saseen et al. (References 18 and 19). In this Discussion section, we have indicated that our results are generally consistent with these prior findings, but we also note some key characteristics that differentiate our study from these previous studies. For example, unlike the present study, Lynch et al. measured only annual all-cause costs, not gout-related costs. Also, prior studies have compared groups of gout patients with 3 or more flares to those with under 3 flares, whereas we compared groups of patients with 0-1 flares, 2 flares, or 3+ flares. We conclude that "Our results serve as a valuable confirmation of these previous observations using a different study population, but we note that it may be difficult to make direct comparisons for gout-related cost estimates between the present study and these previous studies due to differences in patient or flare identification algorithms and differences in definitions for cohort assignments."

Reviewer: 2

I do not know why the authors collapsed zero flares and one flare. I can understand 3+ collapse, but if they want to make the point that avoiding flares is cost-effective - they need to break out the zeros

and ones. I am willing to re-look at it if they do this.

We agree with the Reviewer that this study did not examine the difference in cost between patients with 0 zero flares or 1 flare. Our purpose in conducting this study was to examine the difference in costs between gout patients with frequent vs. infrequent gout attacks. We did not seek to examine whether the occurrence of a single gout attack over a one year period led to increased costs compared to patients without any gout attacks. Therefore, we felt it appropriate to group the 0 and 1 flare patients together in a cohort of patients with infrequent gout attacks. Other studies investigating this question (Lynch et al. and Saseen et al., References 18 and 19) have also grouped patients with infrequent gout attacks together into one cohort. These prior studies actually grouped patients with 0, 1, or 2 gout attacks together into 1 cohort, for comparison with the frequent (3+) gout attacks cohort. Also, urate-lowering therapy is typically recommended for patients with multiple gout attacks, so we felt it appropriate to group the 0 and 1 flare patients together due to this similarity in pharmacological management strategy. In initial exploratory analyses we also found that characteristics were similar between patients with 0 flares and 1 flare in this population. Overall, we feel the study design employed supports the conclusions we have stated at the end of the Discussion: "In conclusion, the results from this study demonstrate that presence of frequent gout flares (2 or more annually) is associated with a substantial economic burden...This suggests significant cost benefit to a gout disease management plan that has a goal of reducing flare frequency to fewer than 2 flares per year, and underscores the importance of prophylactic therapy to control sUA levels and reduce flares." We have further updated text throughout the manuscript to more clearly convey the main objective of this study, and have added a caveat in the limitations section that we did not determine here whether avoiding just one flare leads to cost savings.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Albert Wertheimer Temple University School of Pharmacy, North Broad Street, Philadelphia, Pennsylvania, USA
<b>REVIEW RETURNED</b>	10-Feb-2015

<b>GENERAL COMMENTS</b>	I can see nothing here that adds to the literature in this field  Specifics:  •They concluded that: "Gout related costs and resources were lower in those with infrequent flares."  That is as earthshaking as saying that two scoops of ice cream costs more than one scoop.  •The serious expense for gout treatment is with the 3 or more flares per year group, BUT that is 3788 out of 102,703 patients or 3.7% of gout sufferers. The authors failed to contrast the total financial burden for gout flare ups against other pathologies so the reader can determine whether this is serious or a petty expense not worthy of consideration.  •In Introduction, page 3: Lab results were obtained for "some" of the patients. Is that 7 or 100,000, or ?
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	<ul style="list-style-type: none"> <li>On page 5, top paragraph: Studies should provide enough info to be replicated by a reader, yet we find: "These data were generated by a combination .....and a variety of other individual-level;;;;" These combinations and varieties must be defined and explained.</li> <li>Is there anyone on this planet who would assume anything other than 3 flares is more costly than 1 or two? (Discussion, page 12.</li> <li>Page 15, line 29: "Finally the analyses in this study were performed using patients enrolled in a managed care plan, and the results may not....." Why not? Some 80% of the US population is enrolled in an MCO</li> <li>The 0-1 flares category is anxiety causing. How can a zero flares person be included in the study population if they had no flares during the year? Maybe they don't have gout.</li> </ul> <p>Overall, my reaction to this mss is "Much ado about almost nothing." There are huge expenses for asthma, depression, low back pain, COPD, hypertension, cancer, diabetes, heart failure, burns, etc. but the authors have failed to show that 3+ gout attacks is in the same league.</p>
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<b>REVIEWER</b>	Karen Rascati Univ. of Texas, USA
<b>REVIEW RETURNED</b>	23-Feb-2015

<b>GENERAL COMMENTS</b>	I still think 0 vs. one flare should have been separated. re-wording to 'frequent flares' helped somewhat
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## VERSION 2 – AUTHOR RESPONSE

Reviewer 1

•They concluded that: "Gout related costs and resources were lower in those with infrequent flares." That is as earthshaking as saying that two scoops of ice cream costs more than one scoop.

We agree with the reviewer that it would be assumed that patients with frequent flares would have higher expenses. However, our study aimed to provide contemporary insight into this question by actually quantifying the expenses and comparing them among different cohorts. As we explain in the discussion section: "Although it might be assumed that patients with frequent flares would have higher costs, our study sought to quantify the health care costs and compare them among different cohorts to understand the magnitude of difference. We found that average annual gout-related total health care costs (unadjusted) were higher among patients with either 3+ flares (\$4,490) or 2 flares (\$2,939) vs. those with 0-1 flares (\$1,792, both comparisons  $p<0.001$ )."

•The serious expense for gout treatment is with the 3 or more flares per year group, BUT that is 3788 out of 102,703 patients or 3.7% of gout sufferers. The authors failed to contrast the total financial burden for gout flare ups against other pathologies so the reader can determine whether this is serious or a petty expense not worthy of consideration.

We agree with the Reviewer that the proportion of patients in our study with frequent flares is low, and we have pointed this out in the Discussion section: "Although the proportion of patients with frequent gout flares (3 or more per year) was relatively small in this population, these patients have a high burden in terms of health care costs and resource use." In our study, average all-cause health care costs among patients in the 3+ flares cohort were \$14,824 during the one year follow-up period (Table 2). To provide additional context, we have added some comparisons to annual all-cause health care costs for some other diseases: "In comparison, prior studies using claims data have reported average annual all-cause health care costs of \$11,182 for patients with irritable bowel syndrome, \$13,548 among type 2 diabetes patients, and \$15,487 for patients with prevalent adult systemic lupus erythematosus." (References 20-22) Therefore, we found that all-cause health care costs for gout patients with frequent flares were within the vicinity of other major chronic conditions.

- In Introduction, page 3: Lab results were obtained for "some" of the patients. Is that 7 or 100,000, or ?

Lab results were available for 14,641 out of the 102,703 patients (Table 1).

- On page 5, top paragraph: Studies should provide enough info to be replicated by a reader, yet we find: "These data were generated by a combination ....and a variety of other individual-level;::;" These combinations and varieties must be defined and explained.

The ethnicity and net worth data were not generated by the authors, but rather were licensed from the KBM Group. We have refined our description of this methodology based on the information that has been made available to us: "Patient ethnicity and net worth information were captured from linked socioeconomic status data, licensed from a commercial firm (KBM Group, Richardson, TX, USA). Ethnicity was assigned based on imputation using Census data specific to geographic location and name recognition algorithms incorporating the first, middle and last names (for example, certain names or prefixes or suffixes of surnames are unique to a given ethnicity). Net worth data were determined using self-report, modeling, and census data."

- Is there anyone on this planet who would assume anything other than 3 flares is more costly than 1 or two? (Discussion, page 12.

As we stated above, although we agree it would be assumed that more frequent flares are more costly, our study sought to quantify the actual differences in costs associated with frequent vs. infrequent flares. Please see our replies to the reviewer's first comment above.

- Page 15, line 29: "Finally the analyses in this study were performed using patients enrolled in a managed care plan, and the results may not....." Why not? Some 80% of the US population is enrolled in an MCO

We agree that since the majority of the US population is enrolled in an MCO, the results from this paper should be largely generalizable to the majority of the population. However, we feel it is prudent to state this limitation, as our results may not be applicable to other populations (for example, the uninsured, or Medicare fee for service.)

- The 0-1 flares category is anxiety causing. How can a zero flares person be included in the study population if they had no flares during the year? Maybe they don't have gout.

To be included in the study, all patients needed to meet the criteria for one of the following patient identification algorithms (as described in the Methods section): Algorithm 1: A patient had  $\geq 1$  medical claim with an ICD-9-CM diagnosis code for gout (274.xx) in any position and  $\geq 1$  pharmacy prescription or medical claim for a urate-lowering medication (allopurinol, febuxostat, probenecid, colchicine, probenecid/colchicine, sulfipyrazone, or pegloticase). Algorithm 2: A patient had  $\geq 2$  medical claims on separate dates with a diagnosis code for gout in any position. Algorithm 3: A patient had  $\geq 1$  medical claim with a diagnosis code for gout in any position and  $\geq 1$  pharmacy or medical claim for NSAIDs or corticosteroids within 7 days of the gout diagnosis.

Therefore, even if a patient did not have flares (which were identified by a separate set of algorithms), they still had to meet one of the above criteria for study inclusion. As the patient identification algorithms required presence of either multiple gout diagnoses or presence of a gout diagnosis and a medication, we feel this approach should lead to increased specificity of patient selection. However, as we indicate in the Discussion section as a limitation, these claims-based algorithms used to identify gout patients were not validated with a medical chart review, and we leave open the possibility of misclassifying a certain proportion of gout patients.

Overall, my reaction to this mss is "Much ado about almost nothing." There are huge expenses for asthma, depression, low back pain, COPD, hypertension, cancer, diabetes, heart failure, burns, etc. but the authors have failed to show that 3+ gout attacks is in the same league.

As discussed above, in comparisons with other diseases, we found that all-cause costs for gout with frequent flares were are within the vicinity of other chronic conditions. We have added these comparisons to the Discussion section. However, we feel it is also important to point out that the objective of this study was not to directly compare gout to other diseases, or demonstrate that gout is more costly than other diseases. Rather, the primary purpose in conducting this study was to quantify the difference in costs between gout patients with frequent flares and those with infrequent flares.

Reviewer 2:

Please leave your comments for the authors below I still think 0 vs. one flare should have been separated. re-wording to 'frequent flares' helped somewhat

We have further investigated the Reviewer's question by performing a subgroup analysis in which we compared gout-related total costs among patients with 0 flares to patients with 1 flare. We found that average gout-related total costs were slightly higher among patients with 0 flares compared to patients with 1 flare (\$2,022 vs. \$1,545,  $p<0.001$ ), but median gout-related total costs were lower among patients with 0 vs. 1 flare (\$175 vs. \$242,  $p<0.001$ ). In comparisons to patients with 2 flares, patients with either 0 flares or 1 flare had significantly lower average and median gout-related total costs (all  $p$ -values  $<0.001$ ). We have added these findings to the Results section. These findings suggest that the cost of gout disease management for patients who experience just 1 flare annually is similar to those who don't experience a flare. In comparison, average annual gout-related total health care costs were about 2-3 fold higher among those with 3+ flares compared to those with 0 or 1 flares, demonstrating that the economic burden of disease for patients with frequent flares is substantially higher than for those with infrequent flares.