**Peer Review File**

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**Reviewer A**

This is an interesting report of drug discovery in rheumatoid arthritis (RA) with joint effusion using existing database.

1. Introduction is lengthy and contains irrelevant topics. More focus on pathophysiology of RA may improve the understanding of the manuscript.
Reply 1: We feel great thanks for your professional review work on our article. We intended to increase the comprehensibility of the article by describing RA in detail, but this may lead to some topics being relatively redundant. As you are concerned, we have removed the content of RA diagnostic methods, which are not closely related to the main content of the article. Instead, we have added a description of the pathogenesis of RA to help us better understand new therapeutic approaches. (see Page 4-5, line 69-79)

2. A related article by Okada Y et al. should be referred (Nature 2014;506(7488): 376-81).
Reply 2: Thank you for your reminding. The article you mentioned is very original and interesting. Through a genome-wide association study meta-analysis, Okada Y et al. identified 42 novel risk loci in RA patients, which may reveal the underlying genes and pathways that contribute to the pathogenesis of RA. Their study and mine are similar in that we both identify key genes in RA, but differ in that our study focus more on RA with joint effusion and further search for possible drugs. As you suggested, we referenced and cited this article. (see Page 11, line 213-216)

**Reviewer B**

The biggest opportunity for improvement is a more detailed analysis in the discussion of the medications discovered through the author's research and methods. The authors should expand on how the classes of drugs identified by their analysis may or may not support this method of drug discovery. For example a more detailed discussion on how this method has identified medications that are, in fact, approved for the treatment of RA. This fact is evidence that this method of drug discovery is effective at identifying drugs for the treatment of RA (such as anti-TNF inhibitors) and potentially can identify novel treatment agents.
Reply 1: Thanks very much for your kind help. Your suggestion really means a lot to us. We

did neglect to give a more detailed analysis in the discussion of the medications discovered through our research and methods. We note that some of the drugs we have identified are not usually used to treat RA, but rather to treat other diseases such as endometriosis, acquired thrombotic thrombocytopenic purpura and age-related macular degeneration. Through our analysis, we believe that some of these drugs may have potential therapeutic value for RA. We have modified our text as advised. (see Page 13, line 251-262)

However, contrastingly, several of the medications identified belong to the class of NSAIDs. The authors pointed out in this introduction that NSAIDs are not recommended as treatment option for RA due to inability to prevent disease progression. This perhaps provides evidence that some medications or medication classes identified by this research may not prove to be the most effective options at treating RA with joint effusion. I think this is an interesting discussion that the authors did not go into deep enough.
Reply 2: Thanks for your reminding. We are making further predictions about drugs for RA based on the available evidence. So further studies are still needed to confirm its feasibility. We think it's really an interesting question about the NSAIDs in RA. Although NASIDs are no longer first-line drugs for rheumatoid therapy, they still have a reliable effect on the improvement of pain and stiffness (Lancet 2010;376:1094-108). If we consider joint effusion as one of the clinical symptoms of RA, then it is possible that these drugs have better efficacy for it. In addition, our study also suggests that it is possible that drugs used in the past to treat RA may improve joint effusion. We have modified our text as advised. (see Page 13-14, line 263-273)

Furthermore, the classes of drugs identified by this research is the really interesting results of this study. These potential novel treatments for RA should be discussed further. Have any of these other agents been studied for RA or other inflammatory or auto-immune conditions? Expanding on these potentially novel treatment agents for RA and whether previous research have studied for RA or similar conditions would be interesting. I would recommend the authors provide more substance and depth to the analysis of the medications identified and their relationship or potential relationship with RA especially the agents which have not traditionally been used to treat RA. The medications discovered by this process is the very interesting aspect of the authors research and I want to learn more about their current or theoretical potential for application in treating this disease!
Reply 3: Thank you very much for your professional advice. This is what you mentioned in your last two suggestions and what we overlooked. We have made changes to the further elaboration of the uncovered drugs. (see Page 13-14, line 251-273)

I recommend the authors review the manuscript for grammatical issues, increase conciseness, and clarify some statements:
Reply 4: Thank you very much for your suggestions on our English grammar. We have made corrections to the phrases you pointed out.
Line 58 - eliminate "Besides", this is not necessary and not usually the type of language that appears in peer-reviewed journals

We have rewritten the sentences (see Page 4, line 59)

Line 62 - authors state RA places a "massive financial..." but the first part of the sentence talks about mortality and not financial impact. I would recommend if the authors state there is a financial impact that they provide explicit evidence for such

We have rewritten the sentences (see Page 4, line 63)

Line 63 "...are not clear now." Rephrase with "unclear." for conciseness

We have rewritten the sentences (see Page 4, line 64)

Line 65 - "significantly important..." - this is redundant, use either significant or important. They mean the same thing

We have rewritten the sentences (see Page 4, line 66)

Line 69 - Don't start a sentence with "And" - just eliminate that word and start the sentence.

We removed this sentence

Line 71 - the authors state diagnostics are of high value... why are they of high value? this is not clear

We removed this sentence

Line 72 - remove "so as", you can just say "given early after diagnosis to delay the progression..." for conciseness

We have rewritten the sentences (see Page 5, line 81)

Line 74 - recommend changing "strong side effects" to "adverse effect profile"

We have rewritten the sentences (see Page 5, line 83)

Line 75 - Improve the long-term -> eliminate "the", this is unnecessary word

We have rewritten the sentences (see Page 5, line 83)

Line 76 - "observe a slowing of" -> change to "slow" for conciseness

We have rewritten the sentences (see Page 5, line 85)

Line 77-79 - this sentence is confusing and I do not follow the authors meaning, would recommend revising this sentence for clarity

We have rewritten the sentences (see Page 5, line 86-89)

Line 82 - change "them much suffering mentally and physically." to "physical and mental suffering." for conciseness

We have rewritten the sentences (see Page 5, line 92-93)

Line 86 - "As is known to all," -> the authors make an assumption here. It may be better to say "One example is" and delete "is a typical example."

We have rewritten the sentences (see Page 5, line 96-97)

Line 87-88 - "has brought a lot of new" -> change to "has brought new" for conciseness

We have rewritten the sentences (see Page 6, line 98)

Line 90 - "the law of the occurrence..." - what law? I am confused by the author's meaning here or unfamiliar with this law

We have rewritten the sentences (see Page 6, line 100-101)

Line 99 - researchers*

We have rewritten the sentences (see Page 6, line 110)

Line 127 - the well-known online... - if this is well-known or used in previous research please include citations

We have rewritten the sentences (see Page 7, line 137)

Line 141 - cutoff were* set

We have rewritten the sentences (see Page 8, line 151)

Line 148 - the FDA

We have rewritten the sentences (see Page 8, line 158)

Line 161 BP, CC, or MF - what do these mean? please include what these abbreviations mean or explain

We have rewritten the sentences (see Page 9, line 175-176)

Line 189 - anti-AMD - what is AMD? please spell out first time using abbreviation

We have rewritten the sentences (see Page 11, line 203)

Line 194 - and cytokine activity...

We have rewritten the sentences (see Page 11, line 208)

Line 202-204 - I don't understand this sentence, please revise for clarity

We have rewritten the sentences (see Page 11-12, line 221-222)

Line 214 - "show" do the authors mean "is associated with"?

We have rewritten the sentences (see Page 12, line 232)

Line 225 - "better clinical benefit" what benefit was seen? what is the outcome the authors are referring to?

We have rewritten the sentences (see Page 13, line 244)

Line 246 - "may be able to expand the initial indications of the drugs to treat RA" - the gold standard for adding indications is randomized, clinical trials. I think this research suggests opportunities for further research in the clinical setting. Going from this research to expanding indications is not something we should be comfortable with yet. The authors do acknowledge that clinical evidence should be used to confirm this evidence so I think this sentence should be reworded because it sounds like the authors are stating this evidence is sufficient to add indication to a drug, regardless of whether further clinical research is conducted.

We have rewritten the sentences (see Page 15, line 288-290)