Reviewer's report

Title: Endothelial nitric oxide synthase gene polymorphisms and risk of diabetic nephropathy: a systematic review and meta-analysis

Version: 2 Date: 6 June 2013

Reviewer: Elias Zintzaras

Reviewer's report:

- There are no guidelines for performing meta-analysis of GAS (especially when the outcome is disease progression).

- ORG uses the raw data, i.e. it uses the genotype distribution of cases and controls. When the outcome is disease progression, it uses the genotype distribution of controls, diseased and severe diseased. Thus, ORG is the valid metric to use for this analysis.

- Zintzaras et al (Genetics in Medicine) investigated the following: 1) the risk of diabetic nephropathy (DN) and 2) the risk of diabetes (DM) leading to severe nephropathy (DSN). This is the valid approach.

- The present paper investigates the risk of DN when Diabetes exists. Note that irrespectively to the genetic influence there is always an increase risk! A diabetic control is always a candidate case for diabetic nephropathy (with chance more than 30%). Thus, the present study is not valid.

- The fact that you publish meta-analysis from 2010 does justify the publication of the paper. Your previous published studies also have many methodological mistakes. Please consult an expert, there is one in Sao Paolo University.

- Even if you consider the false analysis, there are many flaws in the paper:

1. What is the mode of inheritance since more than one genetic model was found significant (additive, dominant or recessive)?
2. What is the differential magnitude of effect between small and large studies?
3. Is there enough evidence to deny of claim association under any genetic model?
4. The issue of multiplicity is not addressed.
5. Funnel plot can be misleading.

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'