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Original Article

CHEK2 mutation and risk of prostate cancer: a systematic review and meta-analysis

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Abstract: Background: CHEK2 encodes for a G2 checkpoint kinase which plays a critical role in DNA repair. Its mutation confers an increased risk of breast cancer. It has also been suggested to increase risks of prostate cancer, but its involvement with this type of cancer has not been confirmed. Methods: We performed a systematic review and meta-analysis to clarify the association between CHEK2 1100delC, IVS2+1G>A, I157T mutation and risk of Prostate Cancer. A comprehensive, computerized literature search of PubMed until December 27, 2014 was carried out. Eligible studies were included according to specific inclusion criteria. Pooled hazard ratio was estimated using the fixed effects model or random effects model according to heterogeneity between studies. Results: Eight eligible studies were included in the analysis, all were retrospective studies. The overall meta-analysis demonstrated that the CHEK2 1100delC mutation (OR 3.29; 95% confidence interval: 1.85-5.85; P = 0.00) and I157T missense mutation (OR 1.80; 95% confidence interval: 1.51-2.14; P = 0.00) was associated with higher risk of Prostate Cancer, and CHEK2 1100delC mutation is irrelevant to familial aggregation phenomenon of prostate cancer (OR 1.59; 95% confidence interval: 0.79-3.20; P = 0.20). The IVS2+1G>A mutation is also irrelevant to Prostate Cancer (OR = 1.59, 95% CI = 0.93-2.71, P = 0.09). None of the single studies materially altered the original results and no evidence of publication bias was found. Conclusion: CHEK2 1100delC mutation and I157T missense mutation in males indicates higher risk of Prostate Cancer, but there's no evidence to prove the CHEK2 1100delC mutation was associated with Familial prostate cancer.

Keywords: Prostate cancer, CHEK2 mutation, risk of prostate cancer

Introduction

Prostate cancer is the most commonly diagnosed cancer and a leading cause of cancer related death in American men, which also strongly affects men all over world [1]. With a more comprehensive understanding of the cancer and new protocols for treatment, the outcome of prostate cancer patients has improved in the past few decades. However, we are still not completely clear of the factors which affect the occurrence and prognosis of patients with prostate cancer. Identifying potential genes that could serve as prognostic factors for prostate cancer patients is crucial for individual screen and treatment. Several genes have been demonstrated to affect the occurrence of different kinds of cancer so far, including BRCA1 for breast cancer [2], TP53 for pancreatic cancer [3] and so on. CHEK2 mutation has been detected to increase risks of cancer, besides breast cancer [4], its involvement with prostate cancer has not been confirmed. With the aim to clarify the association of CHEK2 mutation with the risk of prostate cancer, we conducted the first comprehensive meta-analysis of published literature on this topic.

Materials and methods

Literature search

A comprehensive, computerized literature search of PubMed and Embase was carried out until January 27, 2015. Potentially relevant studies were identified using "prostate cancer" (i.e., "prostate cancer," "prostate carcinoma," "prostate neoplasm") and "CHEK2" groups of search terms. The references from relevant papers, especially from review articles, were

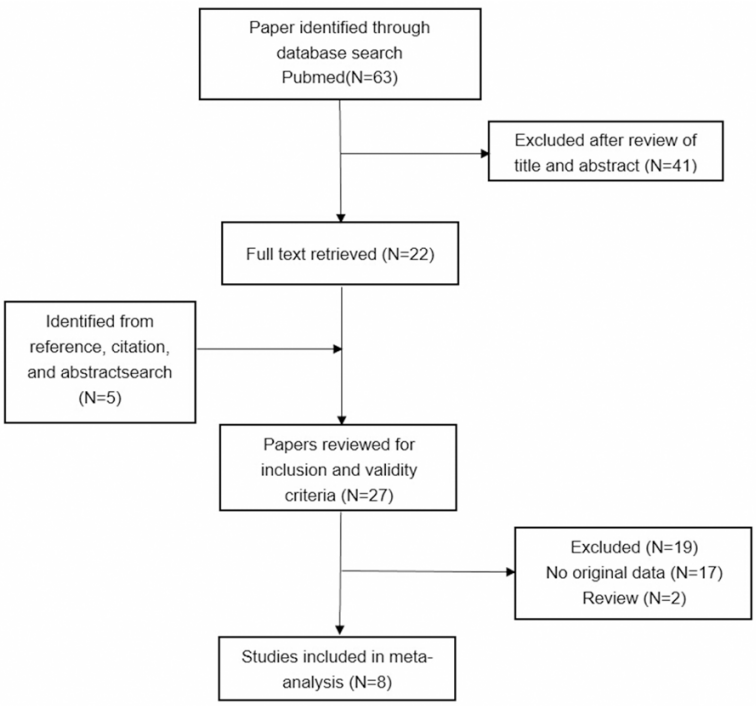

Figure 1. The literature search process. Notes: 63 studies were identified in the primary literature search. 27 potentially relevant studies were further evaluated and eight studies were finally included in the analysis according to the inclusion criteria.

checked to identify studies overlooked in the original search. This systematic review and meta-analysis was planned, conducted, and reported in adherence to the standards of quality for reporting meta-analyses. Studies meeting all of the following inclusion criteria were deemed eligible and included in the analysis: (1) published in English, (2) case-control studies, (3) explored the mutation type of CHEK2 and (4) explored the relation between CHEK2 mutation and whether patients in their studies suffer from prostate cancer. All studies that did not satisfy the inclusion criteria as well as any data obtained from reviews, animal experiments, or cell line studies were excluded. Study quality was assessed using the Newcastle-Ottawa Scale. A flowchart of the literature search, study selection, and results of each step is presented in **Figure 1**.

Data extraction and outcomes

In order to ensure homogeneity of the data gathering and to preclude subjectivity in the data collection and entry, two reviewers independently assessed studies for inclusion, and disagreements were resolved through open discussion. The following information about each study was recorded: first author names, journal and year of publication, patient nationality, total number of patients, median age of patients at diagnosis, the median stage, type of mutation and number of CHEK2 mutation patients.

Statistical analysis

First, we assessed the heterogeneity between studies using the Q-test and I^2 statistic to measure the proportion of total estimate variation that was attributable to study heterogeneity, and either a *P*-value <0.05 or I^2>57% was considered statistically significant. The pooled OR was estimated using the fixed effects model unless heterogeneity was found and was unexplainable, in which case, the random effects model was applied. We used the fixed effects model to analyze the relationship between CHEK2 1100delC mutation and the risk of Prostate Cancer as the heterogeneity between studies was not statistically significant (I^2 = 0.0%; P = 0.76). And the fixed effects model was also applied to further analyze the relationship between CHEK2 1100delC mutation and familial aggregation phenomenon of prostate cancer as the heterogeneity between studies was not statistically significant (I^2 = 0.0%; P = 0.49). This analysis aimed at finding whether family cases had a higher possibility of CHEK2 1100delC mutation than the unselect cases or cases without family history. We also performed a sensitivity analysis by removing each individual study from the meta-analysis. Several methods were used to assess potential publication bias. Potential bias of publication was examined by using the Begg funnel plot and Egger linear regression test (All reported *P* values were two-sided, and *P* values <0.05 were considered statistically significant). We also used the similar methods (fixed effect model) to analysis the relationship between I157T or

Table 1. Studies included in this meta-analysis

Study	Country	Number of patients	Mean age of diagnosis age, years	Number of controls	Family cases	Mean age of diagnosis family cases age, years
Seppala (2003)	FIN	657	69	480	120	62
Dong (2003)	USA	876	/	423	298	/
Johnson (2005)	UK	36	/	155	/	/
Wagenius (2006)	SWE	399	63	305	254	65
Weischer (2007)	DK	116	/	4115	/	/
Cybulski (2013)	POL	4162	69	3956	412	/
Wu (2006)	USA	84	/	95	/	/
Daphne (2007)	USA	79	57	2105	/	/

IVS2+1G>A mutation and the risk of prostate cancer. All statistical analyses performed in this study were carried out using Stata software (v 12.0; StataCorp LP, College Station, TX, USA).

Results

The literature search process and the result of each step are presented in **Figure 1**. Studies were identified in the primary literature, of which 31 potentially relevant studies were further evaluated after review of their titles and abstracts. A total of eight studies meeting the inclusion criteria were finally included in this study. The main characteristics of the eligible studies, all of which were retrospective cohort studies, are shown in **Table 1**. The analyzed studies were published between 2003 and 2013. Six studies [5-10] reported the relationship between CHEK2 1100delC mutation and the risk of prostate cancer (or sufficient data by which these could be calculated, while four of them [5, 6, 8, 9] analyzed the CHEK2 1100delC mutation in family prostate cancer cases in particular. All of the six studies presented a less CHEK2 1100delC mutation than wild type rate. Moreover, Four studies [6, 9, 11, 12] contain the data of CHEK2 I157T missense mutation and only two studies [8, 9] analysis the IVS2+1G>A mutation. Data on the CHEK2 mutation associated with the prognosis of these patients were also recorded. However, we were unable to obtain sufficient data to render any further analysis.

Figure 2A presents a forest plot of meta-analysis for the CHEK2 1100delC mutation and risk of prostate cancer, including OR, 95% CIs, and the weight of each study in the analysis. The control cases in this analysis were people without evidence of prostate cancer. As the heterogeneity between studies was not statistically significant (I^2 = 0.0%; P = 0.76), the fixed effects model was applied. The combined OR was 3.29 (95% CI: 1.85-5.85; P = 0.00). To further test the robustness of our study, we performed publication bias analysis by Egger's or Begg's test (**Figure 3A**) and found no evidence of publication bias (P = 0.13). The result indicates that CHEK2 1100delC mutation correlates with a higher risk of prostate cancer. **Figure 2B** presents the forest plot of meta-analysis for the relationship between CHEK2 1100delC mutation and family prostate cancer cases, the control cases in this analysis were unselect or patients without family history, also including OR, 95% CIs, and the weight of each study in the analysis. As the heterogeneity between studies was also not statistically significant (I^2 = 0.0%; P = 0.49), the fix effects model was applied. The combined OR was 1.34 (95% CI: 0.70-2.55; P = 0.38). We also performed a publication bias analysis by Egger's or Begg's test (**Figure 3B**), which showed no evidence of publication bias (P = 0.50). Thus, the CHEK2 1100delC mutation was associated with higher risk of Prostate Cancer, but it is irrelevant to Familial aggregation phenomenon of prostate cancer. To further test the robustness of our study, we also performed sensitivity analysis by omitting one study each time. We found that no single study altered the original results significantly.

Figure 2C and **2D** show the forest plot of meta-analysis for the CHEK2 I157T missense mutation and IVS2+1G>A mutation and their related risk of prostate cancer, both of the analysis' heterogeneity between studies which included in these two analysis was not statistically sig-

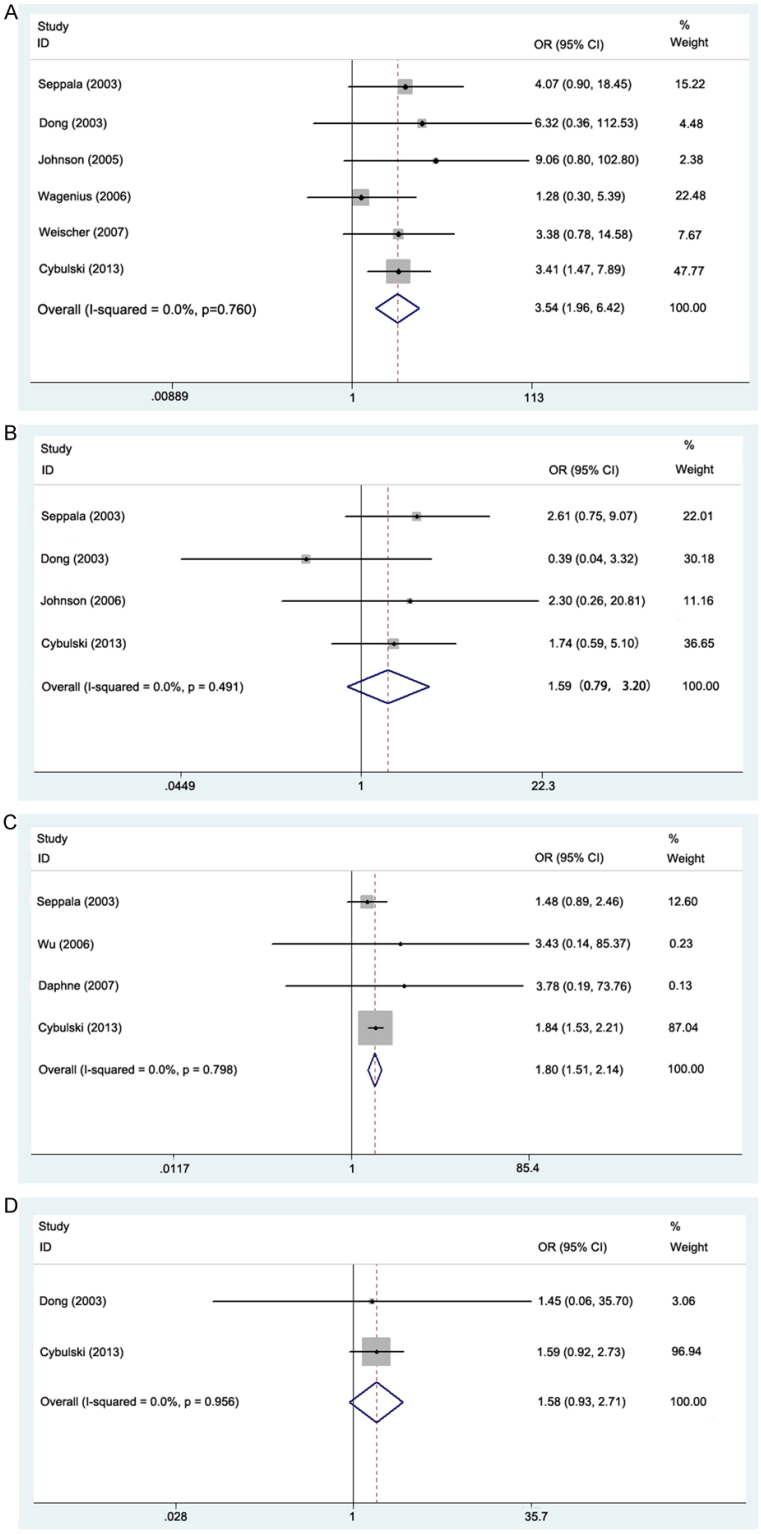

Figure 2. A. Individual study and overall ORs of relationships between CHEK2 1100delC mutation and the risk of prostate cancer. B. Individual study and overall ORs of relationship between CHEK2 1100delC mutation and family prostate cancer cases. C. Individual study and overall ORs of relationships between CHEK2 I157T missense mutation and the risk of prostate cancer. D. Individual study and overall ORs of relationship between CHEK2 IVS2+1G>A mutation and family prostate cancer cases.

nificant. Four studies examining the association between the CHEK2 I157T variant and prostate cancer were included. The Q-test of heterogeneity was not significant. Using the fixed effects model, we found an association of the CHEK2 I157T variant with prostate cancer (OR = 1.80, 95% CI = 1.51-2.14, P = 0.00). A forest plot (**Figure 2C**) showed that the distribution of the ORs from individual studies in relation to their respective standard deviation was symmetrical in the funnel plot. The Egger's test provided no evidence of publication bias in four reviewed studies (t = 0.35, P = 0.76), and Begg's funnel plot with 95% confidence limits was show in **Figure 3C**. Similarly, two studies examining the association between the IVS2+1G>A mutation and prostate cancer were included. The Q-test of heterogeneity was not significant. Using the fixed effects model, we found an association of the IVS2+1G>A mutation with prostate cancer (OR = 1.59, 95% CI = 0.93-2.71, P = 0.09). A forest plot (**Figure 2D**) showed that the distribution of the Ors from individual studies in relation to their respective standard deviation was symmetrical in the funnel plot. The Begg's funnel plot with 95% confidence limits was show in **Figure 3D**. Thus, the CHEK2 IVS2+1G>A mutation was associated not with the risk of Prostate Cancer.

Discussion

The checkpoint kinase 2 (CHEK2) gene which located on chromosome 22q is a tumor suppressor which participates in the DNA Damage signaling pathway [13]. CHEK2 is activated in response to

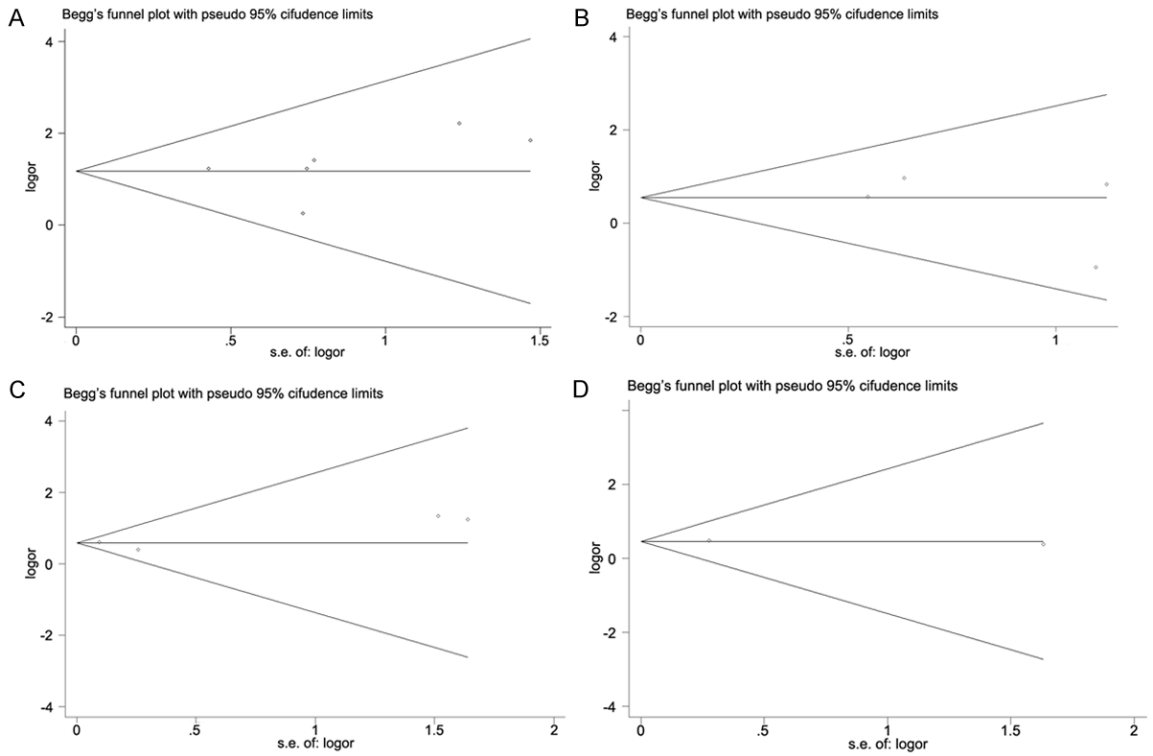

Figure 3. A. Test of publication bias of the nanlysis of CHEK2 1100delC mutation and the risk of prostate cancer. B. Test of publication bias of the nanlysis of CHEK2 1100delC mutation and family prostate cancer cases. C. Test of publication bias of the nanlysis of CHEK2 I157T missense mutation and the risk of prostate cancer. D. Test of publication bias of the nanlysis of CHEK2 IVS2+1G>A mutation and family prostate cancer cases.

various DNA-damage agents in an ATM-dependent fashion. CHEK2 spans 50 kb and contains 14 exons. It is phosphorylated and activated following DNA damage, resulting in cell cycle arrest and apoptosis [14, 15]. CHEK2 mutation have been found to be associated with several types of cancer. Numerous aberrations of CHEK2 gene which contains 1100delC mutation have been observed in several human malignancies, include prostate cancer [16], breast cancer [17, 18], bladder cancer [19, 20], colorectal cancer [21-23] and so on. However, breast cancer is the only one which has been identified associated with CHEK2. Previous studies showed that there are three common variants of CHEK2 mutations present in nearly 5.5% of the population, among them, 1157 T, 444+1G>A and 1100delC were the most common type of mutation [24-26]. In particular, recent publications have addressed the relationship between the CHEK2 mutation in breast cancer. Previous studies showed a frequency of 0.7% in Northern and Western European populations which confer an two fold increased risk of breast cancer to female heterozygous carriers [27]. Moreover, even though the function and mechanism of CHEK2 gene in the human body has not yet been elucidated completely, we can still affirm the value of CHEK2 from previous studies. However, although there is an abundance of information on association of these genomic changes and clinical outcomes, in prostate or other style cancer, data on their distribution about morbidity are limited. Some studies found that in prostate cancer, CHEK2 1100delC mutation is associated with a higher probability of prostate cancer. However, other studies found that CHEK2 1100delC mutation cannot predict patients' risk of suffer from prostate cancer, even though most studies observe a moderately elevated of morbidity in unselect cases or family cases. Besides the CHEK2 1100delC mutation, few studies clearly expounds the association between CHEK2 I157T missense mutation or IVS2+1G>A mutation and their related risk of prostate cancer. Due to the results from previous studies are inconclusive, we performed a systematic review

and meta analysis to clarify the relationship between CHEK2 1100delC mutation, CHEK2 I157T missense mutation or IVS2+1G>A mutation and the risk to suffer from prostate cancer and familial aggregation phenomenon of prostate cancer. In our analysis, we formulate a unified standard. Eight eligible studies with CHEK2 mutation were included in this study. Finally, we came to the conclusion that CHEK2 1100delC mutation and CHEK2 I157T missense mutation was associated with higher risk of prostate cancer. Due to the limited data, we can't affirm CHEK2 IVS2+1G>A mutation and the risk of prostate cancer. But we can still certain that CHEK2 is indeed related to the occurrence and development of prostate cancer cells, its mutation is a risk factors to enhance the the risk of prostate cancer in a patient's life. Moreover, we also analysis the relationship between CHEK2 1100delC mutation and familial aggregation phenomenon of prostate cancer, using four studies which published relevant data and found that there is no statistical significance between CHEK2 1100delC mutation and family cases (**Figure 2B**). Due to the limited data, we can't analysis the relationship between familial aggregation phenomenon of prostate cancer and CHEK2 I157T missense mutation or IVS2+1G>A mutation.

In our meta-analysis, all of the eligible studies which included the four analysis didn't exist heterogeneity, which means higher credibility. But there are still many problems exist in this study. Even though all studies investigated the pathogenic mutations in the CHEK2 gene, but they didn't use exactly the same method. So there were tremendous variation exists in the experimental procedures, which may influence the results and in part the observed heterogeneity. For example, when restricted to via allele-specific oligonucleotides PCR, the heterogeneity between studies may reduce. The clinical significance of this study includes: First, this analysis solved the contradiction result which exist in previous researches, which confirmed that CHEK2 mutation play an important role during the incidence of prostate cancer. CHEK2 1100delC mutation or CHEK2 I157T missense mutation means higher risk of getting prostate cancer. Second, for patients with the CHEK2 mutation, they should receive more positive prostate cancer screening in order to achieve timely treatment to have a better prognosis. Third, CHEK2 mutation and its downstream signaling pathways may become a treatment target in the future.

Our study is not devoid of limitations. First, the number of studies included in our analysis was small, and all of the included studies were retrospective, indicating low levels of evidence in evidence-based medicine. Second, our meta-analysis was based on data only from studies meeting our inclusion criteria, and there were many other published studies that did not meet these criteria. In addition, we could not obtain updated data on individual patients. The use of individual patient data could further enhance the accuracy and reduce the uncertainty of our estimates. Third, all the tissues in our analysis were from patients with high prostate cancer burden countries, which may influence the applicability in other races. Finally, publication bias may also be a concern. It was unavoidable that some data would remain unobtainable even after we tried to identify all relevant information. However, after examining the Begg funnel plots and performing the Egger linear regression test, we found that the association between CHEK2 mutation and clinical outcome remained unchanged.

Conclusion

Our meta-analysis supports the candidacy of CHEK2 1100delC mutation and CHEK2 I157T missense as tumor susceptibility genes in prostate cancer. And CHEK2 1100delC mutation is irrelevant to familial aggregation phenomenon of prostate cancer and the CHEK2 IVS2+1G>A mutation is also irrelevant to Prostate Cancer. However, 1100delC mutation or I157T missense of CHEK2 can be an important factor of suffering from prostate cancer in their life. What's more, patients with the CHEK2 1100delC mutation or CHEK2 I157T missense which responsible for higher cancer burden should receive more positive prostate cancer screening in order to achieve timely treatment.

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Disclosure of conflict of interest

None.

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