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ORIGINAL ARTICLE

Expression and significance of PAX8 gene in ovarian cancer based on Oncomine database Meta-analysis

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Abstract

Objective Although great progress has been made in the diagnosis and treatment of ovarian cancer, this disease is still the leading cause of death due to female reproductive system tumors. It has been reported that the paired box 8 (*PAX8*) gene is involved in the occurrence and development of a variety of human tumors. However, few researchers have investigated this phenomenon in detail.

Methods Here, the BioGPS database was used to analyze the expression of the *PAX8* gene in normal tissues. The Oncomine database was used to search for *PAX8* gene information, and the findings were analyzed via a meta-analysis with regard to the significance of this gene in ovarian cancer. The Kaplan-Meier Plotter database was used to analyze the prognosis of patients with ovarian cancer. The Cancer Cell Line Encyclopedia (CCLE) was used only for obtaining cell line analysis data regarding the *PAX8* gene.

Results The relevant results of the BioGPS database analysis showed that *PAX8* is not expressed or under-expressed in normal ovarian tissues. Oncomine data showed 454 different results; there were 417 study samples in total, with 9 results showing a significant statistical difference in *PAX8* expression, 5 of which were related to high expression of *PAX8* and 4 of which were related to low *PAX8* expression. Cell line analysis data of the PAX8 gene obtained from CCLE showed high expression in ovarian cancer, which is consistent with the high expression of *PAX8* in ovarian cancer research found using the Oncomine database. The Kaplan-Meier Plotter database showed that the expression level of PAX8 had a significant effect on the overall survival time of patients ($P = 0.042$). Compared with the low expression group, the overall survival time of ovarian cancer patients in the high expression group of PAX8 was significantly low ($P < 0.05$).

Conclusion Through an in-depth study of the gene information of ovarian cancer-related genes using the gene chip data in the Oncomine database, it was concluded that PAX8 is highly expressed in ovarian cancer tissues and directly correlates to the prognostic survival of ovarian cancer patients. These findings provide an important basis for the development of clinical gene-targeted cancer therapeutic drugs.

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Ovarian cancer (OC) presents a serious threat to women's health and is considered the third greatest threat to female reproductive health following cervical and endometrial cancer. Due to the difficulty that exists in its early detection and the lack of effective of prognosis determination, it has the highest mortality among the most common reproductive cancers [1–3], not only posing a great economic burden to patients' families and society, but also putting significant pressure on the patients' physical and mental state.

With the development of a social economy and the progress of medical science, technology, instrumentation, and diagnostic methods, the incidence of OC has improved significantly [4]. In addition, technology for tumor detection is in development. By studying the mechanism of OC development at the molecular level and determining the genes highly expressed in OC, further research and development of new drugs targeting these genes can be conducted, thus raising the survival prognosis of patients with OC [5]. The paired box 8 (*PAX8*) gene plays an important role in promoting the development of the Müllerian system in female reproductive organs. It

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is a restricted cell transcription factor, which also exerts additional effects on OC tissue [6–7]. The *PAX8* gene was first described by scholars in the study of Müllerian tube source tumors with differentiating gastrointestinal metastatic carcinoma [8–9] and showed that *PAX8* is highly expressed OC tissue and not expressed in digestive system tumors [10–12]. The *PAX8* gene is highly sensitive and specific in the diagnosis of tumors in the reproductive system [13–14]. However, there is no systematic study that has been conducted on the *PAX8* gene in OC.

This study uses the Oncomine database, BioGPS database, Kaplan-Meier Plotter database, and Cancer Cell Line Encyclopedia (CCLE) to conduct a meta-analysis of PAX8 expression in OC tissue to assist further research on the role of PAX8 in the occurrence, development, and prognosis of OC.

Materials and methods

BioGPS database analysis

The expression of PAX8 gene in normal human tissues was analyzed by using the BioGPS database platform (http://biogps.org).

Oncomine database analysis

The Oncomine database (http://www.oncomine.org) currently collects 715 gene expression data sets and 86,733 cancer tissue and normal tissue samples, and the number of genes is increasing. The database is comprised of multiple gene chip databases and integrated databases, and is currently the largest database platform in the world. Through this database, gene differential expression analysis, co-expression analysis, and meta-analysis of various common cancer tissues and normal tissues can be achieved. The Oncomine database platform meets the need for gene chips by setting constraints. The settings for this research study were: (1) "Cancer Type: Ovarian Cancer"; (2) "Gene: *PAX8*"; (3) "Data Type: mRNA"; (4) "Analysis Type: Cancer *vs.* Normal Analysis"; (5) Threshold setting conditions (P value < 1E-4, fold change > 2, gene rank = top 10%). The corresponding results are described in a box chart.

Cancer cell line encyclopedia database analysis

The Cancer Cell Line Encyclopedia (https://portals.broadinstitute.org/) was used for cell analysis of *PAX8* genes.

Kaplan-meier plotter database analysis

An online survival analysis was performed by using the Kaplan-Meier Plotter database (http://kmplot.com/analysis/). The screening conditions were as follows: (1) "Cancer: Ovarian Cancer"; (2) "Gene: *PAX8*"; (3) "Survival: PFS"; (4) "All."

Results

PAX8 gene expression in normal human tissues

Results from the BioGPS database analysis showed that *PAX8* was not expressed or under-expressed in normal ovarian tissue. Although its high expression was found in thyroid tissue, low expression or non-expression was found in the other tissues of the body (Fig. 1).

Expression of PAX8 in common tumor types

Oncomine showed data for 454 items of different types. Of these, there were 9 tumor types presenting statistically significant *PAX8* expression levels; 5 of which demonstrated high expression levels of *PAX8*, while 4 demonstrated low expression levels (Fig. 2).

Expression of PAX8 in OC

Based on the Oncomine database results, it can be determined that, since 2004, a total of 5 studies involving the comparison of PAX8 expression in OC tissues and normal tissues were conducted. In total, 417 samples—including ovarian serous carcinoma and ovarian clear cell carcinoma—were compared with those of normal tissue. Such articles are published in journals, such as the British Journal of Cancer [15], Cancer Research [16–17], Cancer Science [18], and Clinical Cancer Research [19]. For the meta-analysis using the Oncomine database, the 5 relevant research results showed that, compared with the normal group, the PAX8 gene had a median rank of 27.0 among all the differentially expressed genes (P = 1.350E-5), meaning that the PAX8 gene was highly expressed in OC (Fig. 3).

Differential expression of PAX8 in different OC gene chips

By using gene chip analysis, various studies [15-19] have shown that PAX8 expression in ovarian tumors is higher than that in the normal tissues (P < 0.001), especially in ovarian serous adenocarcinoma, and it is significantly higher in ovarian clear cell carcinoma (Fig. 4).

Results from the CCLE analysis of PAX8 genes

Results from the CCLE analysis of *PAX8* genes show that in cancerous tissue, 37 classes of *PAX8* gene-expressing cell lines exist, showing different degrees of expression; OC ranked third place, confirming an increased expression in ovarian tumor tissue. These findings comply with the high expression of PAX8 in OC seen in the Oncomine database (Fig. 5).

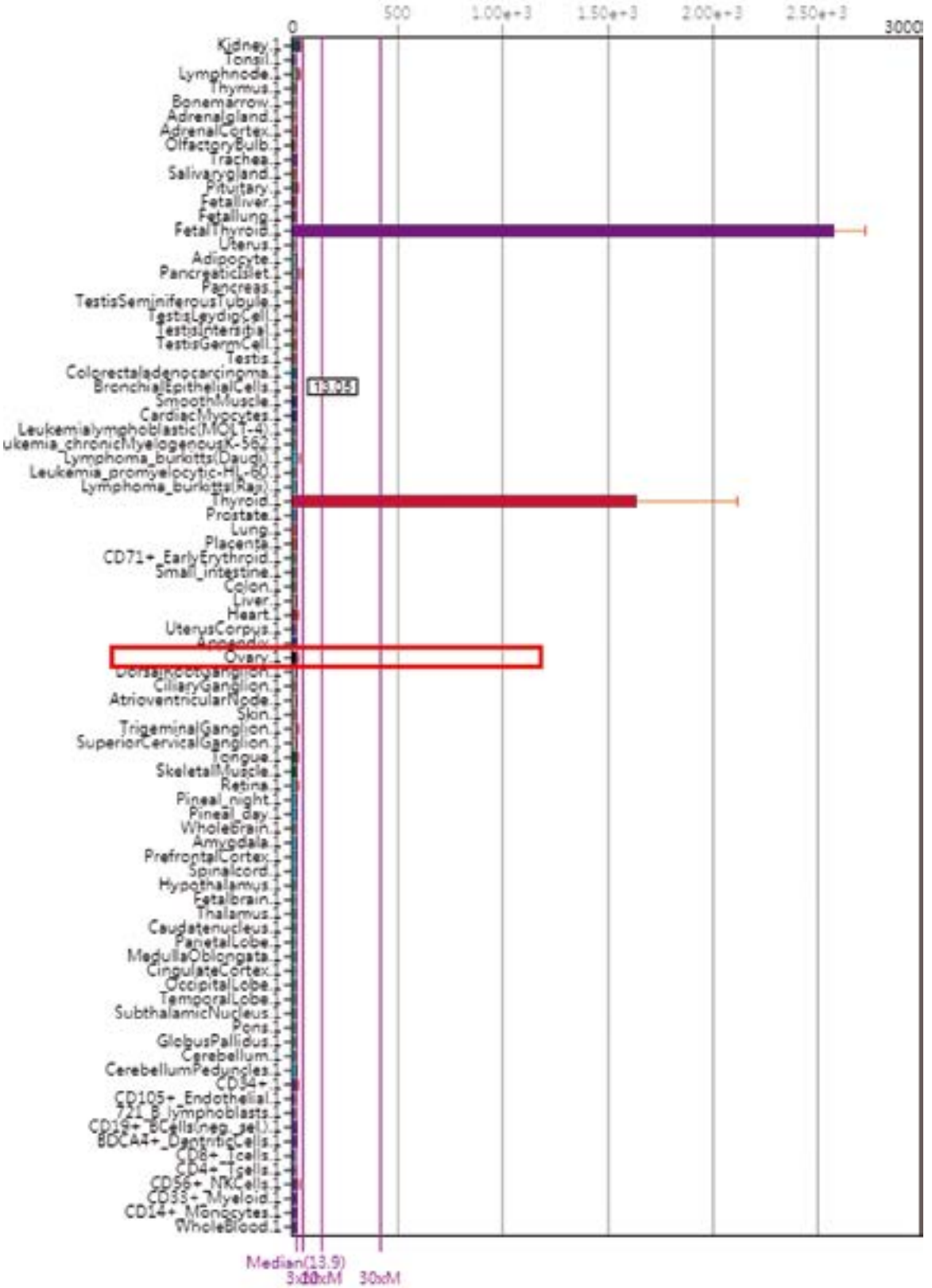

Fig. 1 Expression of PAX8 in normal human tissues

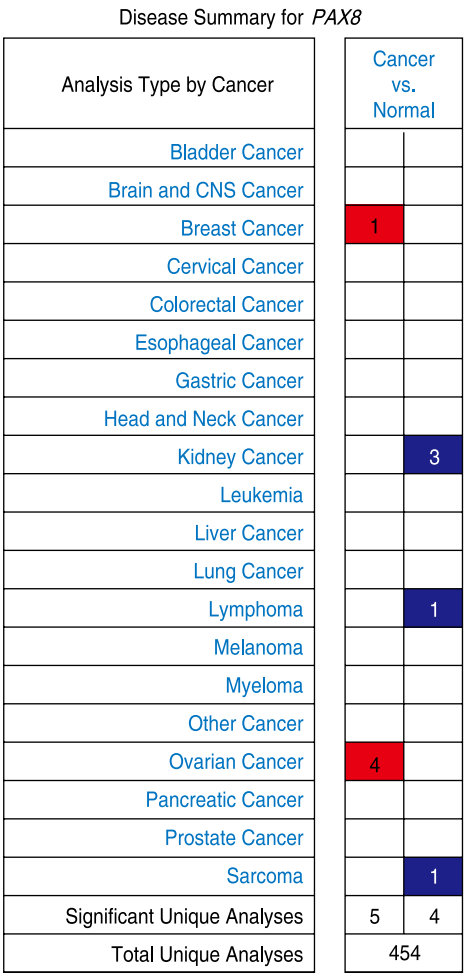

Fig. 2 Expression of the PAX8 gene in all tumor types

Relationship between PAX8 and survival prognosis of OC patients

Results from the Kaplan-Meier Plotter database showed that the expression level of *PAX8* had a significant effect on the total survival time of patients (P = 0.042). Compared with the low expression group, the total survival time of patients in the group with high PAX8 expression was significantly reduced (Fig. 6).

Discussion

OC, as one of the most common malignancies in the world, has a high incidence in female reproductive systems and a corresponding high mortality rate. According to epidemiological statistics, the incidence of OC is increasing slightly [20–21]. Meanwhile, the survival prognosis of OC is very poor; the 5-year survival rate is less than 30%. However, as these tumors have been studied at the molecular level, gene-targeting therapy has become one of the most promising treatments for tumors at present. With the increase in research concerning OC at the molecular level, it has been found that CP, WFDC2, CELSR2, and several other genes associated with OC are of great importance for improving the prognosis of the patients suffering from OC, and are also key factors in the future development of gene-targeting drugs [22–23]. Therefore, the study of key genes related to the occurrence, development, and prognosis of OC has clinical significance for the treatment of OC and the improvement of the survival prognosis of patients suffering from it, which has been a hot topic in recent years.

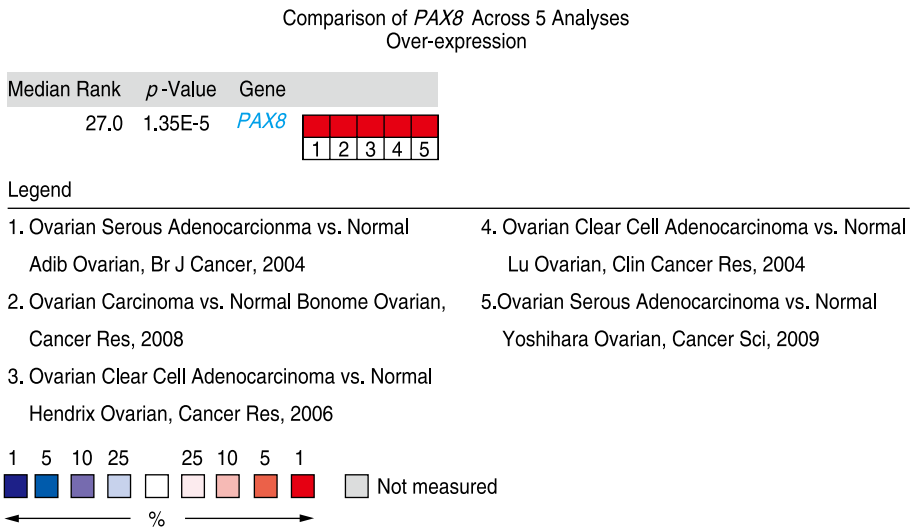

Fig. 3 Summary expression of PAX8 in ovarian cancer research

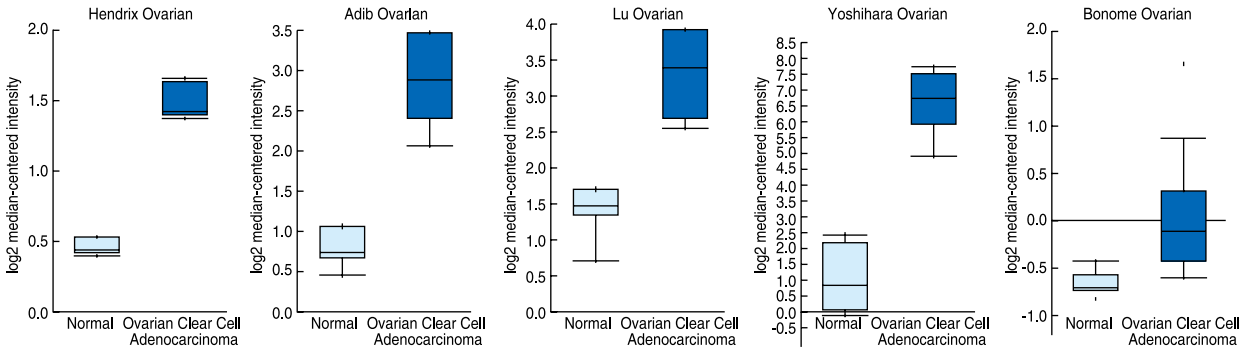

Fig. 4 Expression of PAX8 in different ovarian cancer research chips

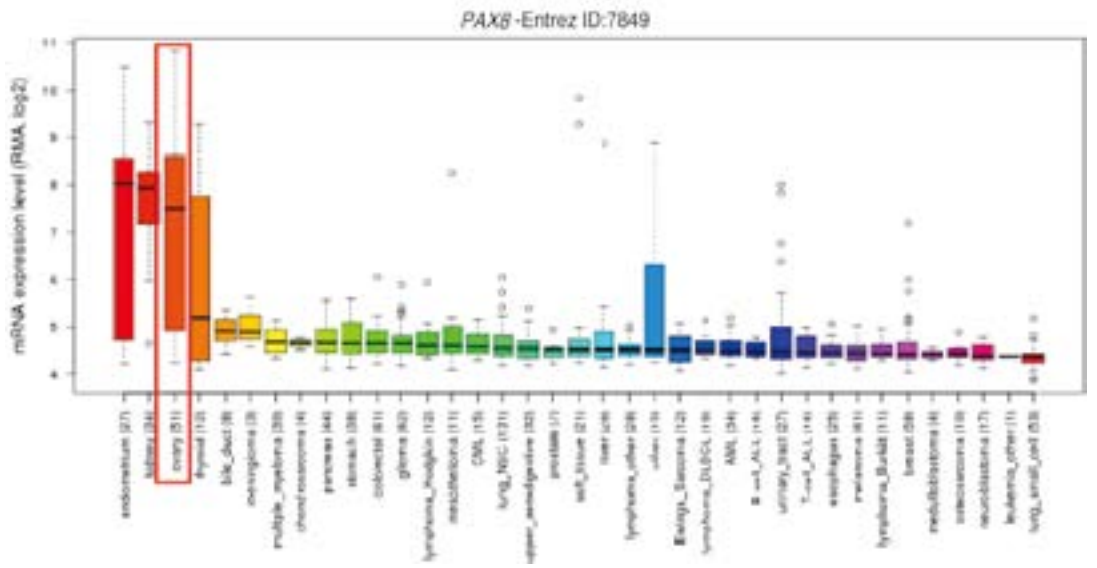

Fig. 5 Results of CCLE analysis of PAX8 gene in cell lines

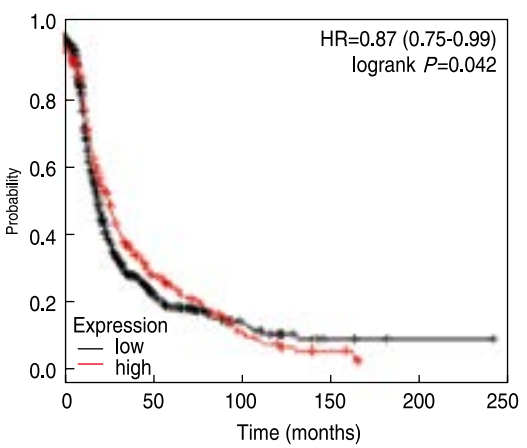

Fig. 6 Relationship between PAX8 expression and prognosis of ovarian cancer survival

PAX8 is a member of the paired box (PAX) family of transcription factors. The family has 9 members; all PAX proteins are composed of 128 amino acids and are located on chromosome 2q13. *PAX8* can attach to specific regions of DNA, having an impact on transcription and gene regulation and control. *PAX8* can control the development of ovarian tissue epithelium and epithelial tumors in the female genital tract with high expression. Moreover, the positive expression rate is low in mucous ovarian tumors, while it is negative in any other benign or malignant tumors of stomatal cells [12]. At present, the exact function of this gene is not quite clear. However, it has been found that *PAX8* has a significant correlation with the development and prognosis of ovarian cancer [24]. Therefore, *PAX8* is a highly specific tumor marker gene that can be used for detecting OC. This is also evident given the high expression of *PAX8* in OC based on the data retrieved from the Oncomine database.

Although previous studies have shown *PAX8* expression increased in various tumor cells and OC groups, the environment and the independent study sample size in these studies was not sufficient, which could easily have led to sampling error. Therefore, the credibility of these researches is not high. The Oncomine database is the world's largest database of gene chip data, which includes information from various tumor gene chips; moreover, all users worldwide have free access to it. The expression of *PAX8* in various tumor tissues can be found by utilizing the Oncomine database. Specifically, the *PAX8* gene was highly expressed in ovarian cancer tissue. In total, there were 9 studies with statistically significant results; among them, *PAX8* showed high expression in 5 studies and low expression in 4 studies. For Oncomine *PAX8* genes, the database was used for meta-analysis. Further results showed high *PAX8* expression in 417 cases among the study samples, with particularly high expression in OC. Moreover, CCLE *PAX8* gene expression data were applied for analysis in OC tissues and cells and showed increased expression. The prognosis of OC patients was analyzed using the Kaplan-Meier Plotter database. The Kaplan-Meier Plotter database is the most extensive database platform covering tumor genes in the world, including 1,816 OC samples. It can be used to analyze prognosis using 54,675 gene chips, and the related retrieval results are reliable. Based on the Kaplan-Meier Plotter database retrieval concerning the *PAX8* gene, it was found that its gene expression and overall prognosis for OC was significantly related to lifecycle ($P = 0.042$), and inclusive outcomes showed that the survival time of patients with high expression of PAX8 noticeably decreased ($P < 0.05$). This consequence may be due to the fact that the PAX8 protein is associated with abnormal regulation of epithelial cells in the ovary, resulting in the occurrence of tumors.

There are numerous sources of gene chip data in this study. Its sample size is large, and the relevant method is highly consistent. The differences in sample size may lead to certain errors; however, this has no impact on the authenticity and credibility of the overall result.

In summary, through the in-depth exploration of the expression data of *PAX8* in OC using the Oncomine database, it has been found that *PAX8* is highly expressed in OC and is directly related to the prognosis of patients with OC. The large sample size of this study helps to avoid the inherent drawback of single-method research and sample size errors and may be of great importance to the treatment of clinical OC.

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Conflicts of interest

The authors declare no potential conflicts of interest.

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