Review Article

Adenoid Cystic Carcinoma of the Lacrimal Gland

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Abstract

Purpose: To explore the various aspects of adenoid cystic carcinoma of the lacrimal gland (LACC), including its clinical features, presentations, genetic factors, as well as current and potential future treatment options.

Methods: A thorough exploration of the literature was conducted by extensively searching the PubMed database. A total of 68 articles with a primary focus on adenoid cystic carcinoma were selected.

Results: LACC is the most frequent malignant epithelial tumor of the lacrimal gland. It is characterized by the symptoms such as pain, progressive swelling of the eye, double vision, and bulging of the eye. Although LACC is a rare tumor, early detection and appropriate treatment are crucial due to its aggressive nature which includes high recurrence rate and a significant risk of mortality. The primary treatment options for LACC involve a wide range of surgical procedures, including orbitotomy, exenteration, and cranio-orbital resection. Neoadjuvant intra-arterial chemotherapy represents the paradigm shift in the treatment of LACC enhancing patient survival when compared to conventional treatments.

Conclusion: The existing literature emphasizes the importance of identifying prognostic factors that can guide treatment decisions and enhance the outcomes for patients with LACC.

Keywords: Adenoid cystic carcinoma, Genetic characteristics, Molecular aspects

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Introduction

Adenoid cystic carcinoma of the lacrimal gland (LACC) is the most frequent malignant epithelial tumor of the lacrimal gland, accounting for 66% of malignant epithelial tumors. In histology, the tumor is composed of basaloid cells that are arranged in three distinctive and prognostically important patterns: cribriform, tubular, and solid that may indicate clinical outcome.[1] The genetic signature of LACC is the translocation of the transcription factor MYB which results in an increased protein expression.[2] Not only does it promote cellular proliferation, but it is also indicative of metastasis making it a good molecular characterization of LACC. Local recurrence and distant metastasis are frequent despite aggressive treatment such as eye sparing surgery or orbital exenteration.[3] Despite the various aggressive treatment modalities, the long-term prognosis of LACC remains poor. Other available treatment options include radiation therapy and chemotherapy. This systematic review aims to comprehensively discuss the clinical features, presentations, genetic and molecular aspects, and current and future treatment options of LACC.

Methods

The current systematic review follows the Preferred Reporting System for Systematic Reviews and Meta-analysis guidelines. An extensive search of the literature was performed using the PubMed database from conception to January 3, 2023. The following MeSH terms: (adenoid cystic carcinoma) AND ("lacrimal apparatus" [MeSH Terms] OR lacrimal gland [Text Word]) were used. A total of 226 articles were

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extracted. Articles focusing on adenoid cystic carcinoma of the salivary glands were excluded. Types of articles included and analyzed were randomized trials, cohort studies, case–control studies, cross-sectional studies, case series, and case reports documenting convincing representation of the various aspects of adenoid cystic carcinoma, from presentation to available treatment options. Studies eligible to be selected were screened by three independent authors for eligibility and a total of 68 papers responding to the inclusion criteria were selected in this review.

Results

The median age of patients with LACC at the diagnosis was 40.4 years. Some cases reported LACC in children as young as 9 years of age.[4,5]

Pain and progressive eyelid swelling were the most common symptoms and were found in more than 73% of cases.[6] Other common symptoms included diplopia,[7-9] proptosis,[8,10-12] and pain, which may be caused by the pressure that is put on the bones and nerves by the tumor,[12-14] and progressive eyelid swelling.[8,12,13] The less common symptoms were the presence of a palpable mass,[14] facial asymmetry,[13] sensory loss,[14] ophthalmoplegia,[10] loss of vision,[10] orbital discomfort,[7] loss of eye motility,[15] facial paralysis,[15] and blurred vision.[16] One study reported an LACC that arose from the lacrimal sac and had presented obstruction of the lacrimal canal and epiphora.[17]

The ophthalmologic examination is usually normal with a normal visual acuity[11,12] except for the presence of a small proptosis and diplopia.[8] In one case, LACC was incidentally found on imaging while the patient was asymptomatic.[8] The ocular examination revealed the presence of a small proptosis and provoked diplopia when the patient was asked to look in a specific direction.[8]

LACC usually arises from the orbital lobe of the lacrimal gland. However, other less common locations have been reported in the literature.

In some cases, primary LACCs were found in the palpebral lobe of the lacrimal gland after a gradually enlarging mass in the upper eyelid was falsely diagnosed with a chalazion.[18,19] Primary adenoid cystic carcinomas originating from the accessory and/or ectopic lacrimal glands of the conjunctiva have also been reported.[20,21]

In rare instances, LACCs were found in tissues in or near the orbits without involvement of the lacrimal gland. Some cases reported the presence of primary LACCs in the lower eyelid after a patient was initially diagnosed with a chalazion.[22,23] Another case reported an LACC arising in the inferior orbit without evidence of lacrimal gland involvement.[24] Schwartz *et al*. reported an adenoid cyst carcinoma in both orbits of the patient. Subsequent work up revealed that the tumor had originally developed in the soft palate and then spread to the orbits via the V1 and V2 nerves.[25]

Local spread and distant metastasis

LACC is an aggressive tumor which frequently spreads to local tissues such as periorbital fat, regional lymph nodes, and distant organs.[8,26] Twelve percent of LACC had disseminated to regional lymph nodes (intra-parotid, submandibular) at the time of the diagnosis. The low incidence of spread to regional lymph nodes suggests that lymph node biopsy is nonessential for the initial assessment of tumor spread.[27] Maamari *et al*. found the presence of distant metastasis of LACC in up to 50% of patients.[8] The most common sites of metastasis were the lungs, bones, liver, and skin.[15]

Zeidan *et al*. reported a case that was diagnosed with a liver metastasis from a primarily LACC 20 years after the initial tumor had been resected.[28] Another case reported a cutaneous metastasis in a patient 21 years after the tumor was initially diagnosed.[29]

Staging

The American Joint Association on Cancer (AJCC) classified LACC into the following tumor stages:

- T1 tumor ≤2.5 cm in greatest dimension limited to the lacrimal gland
- T2 tumor ≤2.5 cm or less in greatest dimension invading the periosteum of the fossa of the lacrimal gland
- T3 tumor between 2.5 and 5 cm in greatest dimension
- T4 tumor >5 cm in greatest dimension.

Prognosis

The median age of survival of LACC has been reported to be 7.6 years.[13] Children affected by adenoid cystic carcinoma have an overall better prognosis than their adult counterparts, with one study reporting the 15-year survival rate at 58%.[30]

The prognosis of LACC is influenced by the tumor stage as classified by the AJCC. Patients with a stage lower than T3 had a worse prognosis than those with a stage of T3 or higher.[31,32]

Other factors such as histological types and treatment options also play an important role in determining the prognosis and will be detailed in later sections.[33,34]

Radiological findings

Computed tomography (CT) scans of patients with LACC showed a soft mass in the lacrimal fossa.[7,13,35,36] Another common observation was the presence of bone erosion.[14,35-37] One study of 17 patients with LACC found that 82.3% of them had invasion of the bones on histopathologic examination, even in the presence of a negative CT scan. Other radiographically reported findings included perineural invasion, tumor calcification, and wedge sign.[14,37] Magnetic resonance imaging can also be used and show mixed signal intensity on T2-weighted images and can be useful in assessing the local spread of the tumor (bone erosion and perineural invasion).[37]

Histopathology

Three main histopathological patterns of LACC have been reported: Cribriform, tubular, and solid (also designated basaloid).[38] It has been shown that histopathologic type

strongly correlates with tumor grade.[32-34] Histopathologically, comedonecrosis was observed on both cribriform and basaloid patterns but was much more prominent in the latter. Analysis of the mitotic activity in the different histologic patterns found that it was significantly higher in the basaloid pattern (median 10.1 mitotic figures per 10 high-power fields) compared with the cribriform pattern (median, 2.9 mitotic figures per 10 high-power fields).[39] Tumors with the cribriform or «Swiss-cheese» pattern have been reported to have a lower grade and a longer survival when compared with the other histologic patterns.[20] Conversely, the basaloid pattern shows an overall higher grade with a shorter survival of 21% at 5 years while the patients whose tumors had no traces of a basaloid pattern in them had a much higher survival rate of 71% at 5 years.[34] The absence of a cribriform pattern and the presence of a basaloid histologic pattern were strongly correlated with poor prognosis.[39]

Genetics

Genetic expression and markers

The mutation profile of LACC is complex. Mutations of common cancer genes including TP53, KRAS (Kristen Rat Sarcoma Viral antigen), and BRAF (v-Raf murine sarcoma viral oncogene homolog B1) are not typically found. One study reported that low expression of B cell lymphoma 2 protein and over expression of TP53 in LACC were related to worse prognosis.[40] A study of high grade of LACC identified miR-140-3p and its target genes as a key player the pathogenesis,[41] which might serve as a potential treatment target. It is thought that several types of cancer, including colorectal, breast, pancreatic, lung, and hepatocellular carcinoma, have been linked to miR-93. Using the qRT-PCR technique, miR-93-5p was overexpressed in tissues and plasma of LACC patients.[42] AKT2 (RAC/beta serine/threonine protein kinase) which is part of the insulin signal transduction pathway, is a target of miR-29a-3p can also potentially play an important role in future target therapies.[43]

Notch signaling pathway, a conserved cell signaling pathway, is essential for development and, when misdirected, promotes tumor growth. The posttranslational modifications of the active Notch receptor, or the notch intracellular domain (NICD), determine the magnitude and length of the Notch response. The overexpression of Notch1 receptor and NICD1, present in some individuals, played a role in the aggressive behavior of LACC leading to a reduced disease-free survival.[44] Another study found that mutations in the Notch pathway genes were present in some samples that were studied yet further research needs to be done to determine potential therapeutic targets.[45]

Apart from Notch signaling, some cell types use the type III receptor tyrosine kinase known as CD117 (KIT) for cell signal transduction. When KIT binds to its ligand, a phosphorylation cascade occurs, activating several transcription factors. Zhou *et al*. found that the P63-/CD117+ pattern was unrelated to histological grade or prognosis in LACC. However, an elevated number of P63+/CD117+ cells were related to worse prognosis in advanced stages. This may be a tool of prognosis assessment.[46]

The MYB and NFIB fusion and its target genes are commonly expressed in LACC and the salivary glands. By activating many MYB-regulated genes, MYB-NFIB fusion promotes cell proliferation, survival, and cell cycle progression. They can potentially serve as diagnostic and predictive biomarkers.[47] Another study also found that LACC was characterized by gene fusions involving MYB, MYBL1, and NFIB.[48] However, a retrospective study conducted in Mayo Clinic explored the incidence of the fusion transcript, t(6;9)(q22-23;p23-24), involving both MYB and NFIB in LACC. This rearrangement was present in 58% of cases but did not show a clinical impact. There was no difference in overall survival in patients with LACC carrying this rearrangement comparing to those who did not.[49]

Finally, to understand the angiogenic properties of LACC, quantitative real-time PCR was used to assess the level of mRNA expression of vascular endothelial growth factor (VEGF). The results showed that VEGF was expressed in almost half cases (46.6%), and it was associated whit intracranial extension and solid histological pattern. In addition, VEGF was a factor of poor prognosis on multivariate analysis. This marker of angiogenesis might play a role as a potential predictive factor for LACC.[50]

Protein expression and markers

A comparative study by Huang *et al*. found that the expression rate of p16 (also called cyclin-dependent kinase inhibitor 2A, CDKN2A, and multiple tumor suppressor 1) in LACC was dependent on the cell type.[51] It was higher in recurrent LACC and unrelated to HPV infection. However, its mechanism of action needs to be further investigated.[52]

A member of the inhibitor of apoptosis family, Survivin, is also known as baculoviral inhibitor of apoptosis repeat-containing 5. The clinicopathological characteristics of cells with LACC were studied by Mulay *et al*.[53] Out of the 55 cases, 31 (56.4%) had Survivin expression in the tumor cells' nuclei. This was correlated with histological markers of a poor outcome and higher expression of markers of apoptosis and proliferation. Another study by Pan *et al*. analyzed the level of this antiapoptotic protein Survivin, in LACC.[54] When compared to controls, the LACC groups' Survivin mRNA and protein expression levels were significantly higher, especially for tumors in the stages 3 and 4 of the TNM classification. Silencing its gene reduced the rate of cell proliferation, documenting its role in the apoptosis pathway. Using extract of Ginkgo biloba on cells of the LACC, Zhou and Zhu reported a significant decrease in Survivin gene expression consequently inducing apoptosis.[55] This finding may have importance in the development of future therapies.

Glial cell line-derived neurotrophic factor (GDNF), GDNF family receptor alpha-1, and RET proteins expression was quantified using immunohistochemistry in LACC.[56] They were expressed in 62.7%, 62.7%, and 54.9% of cases, respectively.

Their presence might be related to perineural invasion and thus tumor recurrence in some cases as RET proto-oncogene plays an important role in cell signaling.[56]

The expression of matrix metalloproteinase (MMP), in particular MMP2 and MMP9 was higher in patients with LACC compared to controls. This was correlated to the number of micro vessel density. Further research need to study its role as a potential diagnostic marker.[57]

Treatment options

The treatment of LACC is challenging and depends on several factors including the stage and location of the tumor, as well as the patient's overall health and medical history. It often requires a combination of surgical procedures, radiation therapy, and chemotherapy. Due to the rarity of LACC, there are limited data available on the best treatment approach for this condition.

Surgery

Surgery is the mainstay of treatment for LACC, with wide local excision being the most common surgical procedure performed. Depending on the size and location of the tumor, different surgical approaches may be employed, including lateral orbitotomy, exenteration, and intracranial or extracranial *en bloc* resection. In some cases, complete removal of the affected lacrimal gland may be necessary, along with the removal of lymph nodes and adjacent tissues. However, when complete resection is not possible, debulking surgery may be performed to reduce the size of the tumor. Finally, the cranio-orbital resection, a surgical technique that involves the removal of the eye, part of the skull, and the surrounding tissues, does not seem to improve the survival of patients with LACC.[58,59] According to the available literature, there is no significant difference in survival rates between patients who underwent cranio-orbital resection and those who underwent other types of surgical resection. Cranio-orbital resection may be necessary in some cases where the tumor has invaded the skull.[60,61]

Radiation therapy

Radiation therapy is often used in combination with surgery to improve the chances of long-term disease control.[58] It may also be used as a single modality in patients who are not candidates for surgery, or as an adjuvant treatment after surgery to reduce the risk of local recurrence.[58,59] Proton beam therapy may be preferred over conventional radiation therapy due to its ability to deliver the higher doses of radiation while minimizing damage to surrounding tissue.[62] Comparative studies showed that the high-dose external-beam radiotherapy needed for LACC can produce significant corneal surface morbidity leading to visual impairment potentially necessitating corneal transplant as well as an increase in incidence in corneal perforation, especially in the first 3 years.[63] Patients undergoing radiotherapy should be closely monitored for corneal complications and provided with appropriate management and support.

Chemotherapy

The addition of chemotherapy to radiation therapy for LACC has been shown to improve disease control and overall survival.[58] The commonly used chemotherapy drugs include cisplatin, carboplatin, and methotrexate. The prospect of neoadjuvant chemotherapy, be it through intra-arterial or intravenous means, shows significant potential in reducing the size of lacrimal gland tumors. This becomes particularly compelling when integrated with eye sparing surgeries.[59] This technique proved to be useful in the treatment of adenoid cystic carcinoma of the salivary gland.[64] Neoadjuvant intra-arterial chemotherapy (nIACC) for LACC was introduced in 1998, in an effort to improve patient survival. The study detailed the treatment of individuals with advanced LACC which involved the administration of intracarotid cisplatin and intravenous doxorubicin, followed by orbital exenteration. Postoperatively, orbital irradiation was conducted, complemented by further intravenous cisplatin and doxorubicin.[65] The intra-arterial delivery of the drug restricts systemic toxicity since a significant portion of the drug is extracted within the tumor's capillary bed, contributing to limited systemic effects.[66] The investigators compared a case series of nine patients using the protocol described above with a series of patients undergoing conventional treatment options.[67] Conventional treatment approach consists of orbital exenteration, with or without the removal of adjacent bone, followed by external-beam radiation therapy.[66,67] Preliminary findings showed that in the group treated with nIACC, the cumulative 5-year rate of carcinoma-specific deaths was 16.7%, notably lower compared to the conventional treatment group (orbital exenteration and radiation therapy), which had a rate of 57.1%.[66,67] Patients treated with nIACC also exhibited a noteworthy reduction in the cumulative 5-year recurrence rate, reporting a rate of 23.8%, as compared to the conventional treatment group of 71.4%.[66,67] Genetic analysis of the tumor tissue obtained by microdissection to identify the potential biomarkers for treatment response found that certain genetic alterations were more commonly found in tumors that had a good response to nIACC.[66] In 2013, Tse's research team detailed the extended outcomes of nIACC among 19 patients. The study emphasized that individuals meeting specific criteria, such as an intact lacrimal artery, no disruption in the bone barrier or tumor manipulation aside from incisional biopsy, and strict compliance with the treatment protocol, displayed better outcomes compared to those who either lacked the lacrimal artery or deviated from the prescribed treatment plan.[68] They documented a 100% 10-year survival rate among the subgroup of patients treated with nIACC who retained an intact lacrimal artery and adhered meticulously to the entire treatment protocol without any deviation.[68] The findings of these reports indicate that incorporating nIACC alongside the traditional method of orbital exenteration and radiation in treating LACC are effective in enhancing overall survival and decreasing disease recurrences.[66-68]

The strategy of the targeted nIACC technique is to deliver the high concentration of chemotherapy to the tumor through an intact lacrimal artery prior to exenteration. This approach helps deliver a concentrated drug like cisplatin, achieving a superior

local drug concentration, resulting in an increased efficacy.[69,70] Targeted nIACC is effective in inducing apoptosis in LACC tumors as high-dose chemotherapy overwhelms the tumor's nucleotide excision repair system preventing DNA replication, leading to tumor regression and an increasing the proportion of tumor tissue exhibiting apoptotic markers.[69] Ultimately, the objective of nIACC is to reduce the size of the tumor and enhance its margin clearance at the time of exenteration enabling a more complete surgical resection and minimize the dissemination of viable tumor cells both before and during surgical manipulation.[69,70] The presence of an intact lacrimal artery is an integral characteristic for optimal treatment option, decreasing the all-cause mortality and recurrence rate compared to patients undergoing nIACC with a nonintact artery disrupted by prior radiation or surgery.[70] The absence of an intact lacrimal artery was seen in patients who had an excisional biopsy. Before surgery, the mass in five of these patients was initially assessed as a pleomorphic adenoma of the lacrimal gland (LGPA), and in toto dacryoadenectomy was performed based on this assessment. Subsequently, during the procedure, nIACC injection was administered despite the artery not being intact.[70] It has been described that successfully extracting both the tumor and its surrounding capsule during the initial surgery plays a critical role in preventing tumor recurrence in the case of LGPA. Excisional biopsy is usually indicated in that case to reduce the risk of recurrence.[71] In fact, full excision, breach of the pseudocapsule, and performing an incisional biopsy were noted to correlate with heightened risks of recurrence and potential malignant transformation.[72] Performing an incisional biopsy was initially thought to increase the risk of recurrence by causing disruption to the pseudocapsule and potential spillage of the tumor cells.[73] However, some studies suggest that a complete surgical removal of the tumor is sufficient to reduce tumor recurrence. For instance, Henderson documented cases of LGPA from the Mayo Clinic, and 14 out of 15 patients who underwent complete resection experienced no recurrence over an average follow-up period of 9.7 years even if they previously underwent incisional biopsy.[74] Another study found that out of 15 patients who had a biopsy prior to surgery of LGPA, 10 later underwent lateral orbitotomy, total dacryoadenectomy, and removal of the biopsy track and no recurrence was observed during a mean follow-up period of 6 years.[72] This report highlighted a significant risk of recurrence when LGPA removal was incomplete, but interestingly, it did not find an increased risk associated with tumor spillage or biopsy procedures.[72] Finally, Rootman *et al*. presented a case of LGPA involving preoperative fine-needle aspiration biopsy followed by en bloc excision through lateral orbitotomy, confirming complete excision through histological examination. There were no signs of recurrence throughout the 15-month follow-up period.[75] Choosing an incisional biopsy as the primary step in addressing epithelial tumors of the lacrimal gland is overall a reasonable approach and should not be contraindicated if there is a suspicion of LGPA.

In addition, IACC could be a viable treatment option for pediatric LACC.[76] Of note, there have been three documented cases where recurrence happened after patients underwent nIACC, followed by surgery and high-dose radiation therapy. One case had diffuse metastasis. The two other reported adverse effects requiring a change of protocol, they later died because of disease recurrence. These instances emphasize the importance of vigilant monitoring for both local relapse and distant metastasis among patients who have undergone nIACC as the part of a trimodal treatment strategy.[77,78] Further studies are needed to confirm these findings and determine the optimal treatment approach for this type of cancer.

Targeted therapy

Targeted therapies, such as tyrosine kinase inhibitors, have been used with some success in treating LACC. These drugs work by blocking specific proteins that promote tumor growth and may be used in cases where the tumor has metastasized or is not responsive to other treatments.[69,79] However, more research is needed to fully understand the role of these therapies in the treatment of LACC.

Future therapy and drug resistance

There is currently no cure for LACC, and the treatment of this disease is complex and requires a multidisciplinary approach. Despite many advancements in treatment, the prognosis for patients with LACC remains poor, with high rates of local recurrence and distant metastasis. Further research is needed to determine the optimal treatment approach for LACC and to develop new and innovative treatment strategies to improve the outcomes for patients.

Some proteins could have a role in resistance to some drugs usually used as a treatment for LACC of which, the ribosomal protein L39-L, forming a part of the 60S ribosomal subunit. The drug-resistant human LACC cell line had a 6.5-fold greater amount of ribosomal protein L39-L transcription than the susceptible cell line through rTPCR analysis.[80]

The expression of programmed cell death ligand 1 (PD-L1) and PD-L2 and the level of CD8-positive T-lymphocyte infiltration can predict how well a tumor will respond to treatment with a class of medications called immune checkpoint inhibitors (ICIs).[81] Low overall tissue expression levels of PD-L1 were found after immunostaining in LACC. PD-L2 expression levels were also generally low. ICIs drugs may not play an important role in the treatment course of orbital adenoid cystic carcinoma.[81]

Research is ongoing to assess the effectiveness of bevacizumab in treating LACC. One study used patient-derived xenografts (PDXs) to evaluate the efficacy of bevacizumab, a monoclonal antibody that targets VEGF.[82] The analysis found that bevacizumab, when intravenously injected at a dose of 5 mg/kg twice weekly for 33 days, was able to significantly reduce the growth of ACC tumors in the PDXs.[82] Moreover, the treatment was well-tolerated, with few side effects reported. The article suggests that bevacizumab may be a promising treatment option for ACC of the lacrimal gland, especially for patients with advanced or metastatic disease. However, further

studies are needed to determine the long-term outcomes and safety of this treatment approach in human patients.[82]

Discussion

Despite LACC being a rare tumor, its early diagnosis and adequate treatment are vital due to its aggressive nature comprising high rates of recurrence and a high mortality rate. The main symptoms of LACC are pain and progressive eye swelling, diplopia, and proptosis. Numerous studies have investigated the link between different histologic patterns of LACC and prognosis and have found a strong correlation between the two. The cribriform pattern was shown to have a good overall prognosis while tumors that had a basaloid pattern had a more reserved prognosis. The main treatment options for LACC encompass a broad spectrum of surgeries, including orbitotomy, exenteration, and cranio-orbital resection. Surgery and radiation therapy should be complimentary as the association of both has shown to decrease the local recurrence rate. In addition, nIACC was shown to further decrease the risk of local recurrence as well as decrease the risk of distant metastasis and should thus be integrated in the overall treatment plan of patients with LACC. Finally, multiple studies have investigated the pathogenesis of LACC on a molecular level and have found multiple pathways that could be used in the future to treat this type of tumor. MiR-140-3p has been found to be a key player in the pathogenesis of LACC. MiR-93-5p miR-29a-3p have also been shown to be overexpressed in patients with LACC. Some pathways such as Notch signaling could potentially be used as a targeted therapy while other receptors while others could potentially be used to diagnose (MYB-NFIB) or to evaluate the prognosis (P63+/CD117+) of LACC. The findings in the literature underscore the importance of identifying prognostic factors to guide treatment decisions and improve the outcomes in patients with this tumor.

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Conflicts of interest

There are no conflicts of interest.

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