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HOT TOPICS IN BREAST CANCER (K HUNT, SECTION EDITOR)

Current Considerations of Breast Implant–Associated Anaplastic Large Cell Lymphoma in Breast Surgery: a Systematic Review

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Abstract

Purpose of Review A systematic review of three databases (PubMed, Scopus, and Google Scholar) was conducted to appraise the current evidence behind the diagnosis and management of breast implant–associated anaplastic large cell lymphoma (BIA-ALCL). The goal is to help patients make informed decisions regarding reconstruction after breast cancer treatment by educating physicians on the nuances of diagnosis and treatment of BIA-ALCL.

Recent Findings Following recent statements by the FDA, BIA-ALCL has recently garnered the attention of both patients and plastic surgeons. To date, BIA-ALCL has been almost exclusively associated with textured implants.

Summary BIA-ALCL is a very rare T cell lymphoma that was first described more than 20 years ago. BIA-ALCL usually follows an indolent course and carries an excellent prognosis if treated promptly. However, the pathogenesis of the disease is unclear, and further studies need to be conducted to better understand the disease.

Keywords Breast implant · associated anaplastic large cell lymphoma (BIA-ALCL) · Anaplastic large cell lymphoma (ALCL) · Breast reconstruction · Breast cancer · Breast implants

Introduction

Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is a T cell lymphoma involving the capsule surrounding breast implants. Since the first case report in 1997, studies have helped to establish the condition as a rare but distinct lymphoma with effective treatment algorithms developed by the National Comprehensive Cancer Network [1–3].

Since silicone gel–filled breast implants were first placed in 1962, implant-based breast surgery has become the number one cosmetic procedure performed in the USA, with estimates indicating that more than 550,000 implants are placed per year [4, 5•, 6]. Worldwide, there is an estimated 10 million patients with breast implants [4].

The first case of BIA-ALCL was reported by Keech and Creech in 1997, and since then, there has been a steadily increasing body of evidence that indicates textured implants may have a causal link to BIA-ALCL. The exact mechanism, however, remains unknown [3, 7]. A Dutch study in 2008 was the first to report on the positive association between breast implants and BIA-ALCL by utilizing its nationwide pathology database, which reported various types of breast pathologies [8•]. The results showed that while the absolute risk of developing the disease is low after implantation due to the rarity of the disease (11 cases reported in 17 years), the odds ratio was 18.2, indicating that patients with implants were much more likely to develop ALCL than those without implants [8•].

Recently, the interest in BIA-ALCL has heightened both in health policy governing bodies and the general public [7, 9]. The FDA issued its first communication warning of the possible association between breast implants and ALCL in 2011 [10]. In 2016, the World Health Organization recognized BIA-ALCL as "a primary effusion lymphoma with an indolent course that can progress to infiltrative disease with mass aggregation in more advanced cases" [11]. In 2018, the FDA issued its fourth safety communication warning of the association, and as of July 2019, there have been 582 cases of BIA-ALCL reported worldwide [7, 12, 13].

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The association has the potential to affect changes in patient care, methods, and materials used in both reconstructive and cosmetic breast surgery. While the exact pathophysiology and prevalence of the condition have yet to be determined, the condition tends to carry an excellent prognosis with appropriate surgical management. Implant-based reconstruction is often included in the list of reconstructive options after mastectomy, and as such, BIA-ALCL is a condition that breast cancer specialists are encouraged to be aware of. In this review, we will examine the available literature regarding BIA-ALCL and discuss possible implications in patients who desire oncologic breast reconstruction or cosmetic breast enhancement.

Methods

A systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [14] (Fig. 1). A literature search was performed in PubMed, Scopus, and Google Scholar using the following keywords: breast implant–associated large cell lymphoma, lymphoma, and breast implants. Additionally, we used the MeSH terms: breast implant, lymphoma, and mammaplasty. We included all prior reviews, case reports/series, and clinical/basic science research. Non-English papers were excluded. All references were manually searched for additional sources.

Results

A total of 1092 results were obtained and 687 non-duplicate articles were included in the title/abstract screen (Fig. 1). A total of 383 articles were included in the full-text analysis. Of the 383 articles, 62 were reviews, 161 were case report/series, 123 were clinical articles, and 37 were basic science articles. A total of 112 articles were included after full-text review.

A total of 91 case reports were reviewed for patient age, affected side, interval from implantation to diagnosis, reason for implant, type of implant, implant volume, affected side, reported symptoms, stage of disease at presentation, treatment modality used, and patient outcomes.

The mean age at diagnosis was 52.5 years, with a range of 24–87 (Table 1). The mean interval to lymphoma diagnosis after implantation was 10.9 years. Cosmetic reasons for implant were more common than reconstruction after breast cancer (52% vs 41%), and there was a slightly higher incidence of right-sided BIA-ALCL. The most common presenting symptom was seroma at 68.1%, followed by lymphadenopathy (14.3%) and both seroma and mass (13.2%). Other presenting symptoms included skin. Most patients presented early at stage I, and only 6% of patients presented as stage III or IV. Pre-existing oncologic conditions other than breast cancer included Li-Fraumeni syndrome, non-Hodgkin lymphoma, intravascular large B cell lymphoma, and systemic ALCL. Three cases were transgender females.

The most common type of therapy utilized was surgery only at 39.6%, followed by a combination of surgery and chemotherapy (21.9%) (Table 2). A combination of surgery, chemotherapy, and radiation was also utilized, and stem cell transplant occurred in 4 patients. In terms of patient outcomes, disease-free survival was the most common at 70.3%. In our review, we identified 5 cases of deaths in the literature with sufficient information to include in the analysis. Type of implant used and implant volume were inconsistently recorded.

Pathophysiology

The breast can be affected by non-Hodgkin lymphomas that may be primary or metastatic in nature. The most common subtypes, accounting for more than 90% of all breast lymphomas, include diffuse large B cell lymphoma and extranodal marginal zone lymphoma [15••]. BIA-ALCL is an extranodal T cell lymphoma [9], which is a very rare subtype of T cell lymphomas.

Several theories exist on the pathogenesis of BIA-ALCL, with chronic inflammation and bacterial infection of the implant being the most common. Interestingly, BIA-ALCL seems to exclusively occur in textured implants, which were developed in the late 1980s to decrease the rate of capsular contracture associated with smooth implants [5•, 16, 17••]. Capsular contracture is thought to be due to a chronic inflammatory reaction resulting in fibroblast proliferation, scar, collagen deposition, and encapsulation [16, 17••]. It was thought that if the implant surface was disrupted by a texturized surface, a less organized capsule scar would form, resulting in decreased capsular contracture [16]. Studies by Hu et al. have demonstrated that the contamination of implants with resultant bacterial biofilm formation contributes to the development of capsular contracture [17••, 18, 19]. Interestingly, cultures indicate that there is a significantly higher proportion of gram-negative bacteria such as *Ralstonia picketti* in BIA-ALCL specimens, while non-tumor capsule contracture specimens have predominantly gram-positive organisms such as *Staphylococcus* [17••]. This indicates that colonization by specific bacteria may trigger selective lymphocyte proliferation and subsequent malignant transformation, leading to an increased risk of malignant transformation [17••, 20].

Genetic studies have revealed similarities between BIA-ALCL and systemic ALCL, including a similar signal responsive transcription factor 3 (STAT3) overactivation, but BIA-ALCL tends to have an indolent course when compared with systemic ALCL, which tends to be an aggressive malignancy with a poor prognosis [21–23]. Also, BIA-ALCL patients have variant HLA A*26 expression when compared with patients with systemic ALCL, which suggests that BIA-ALCL

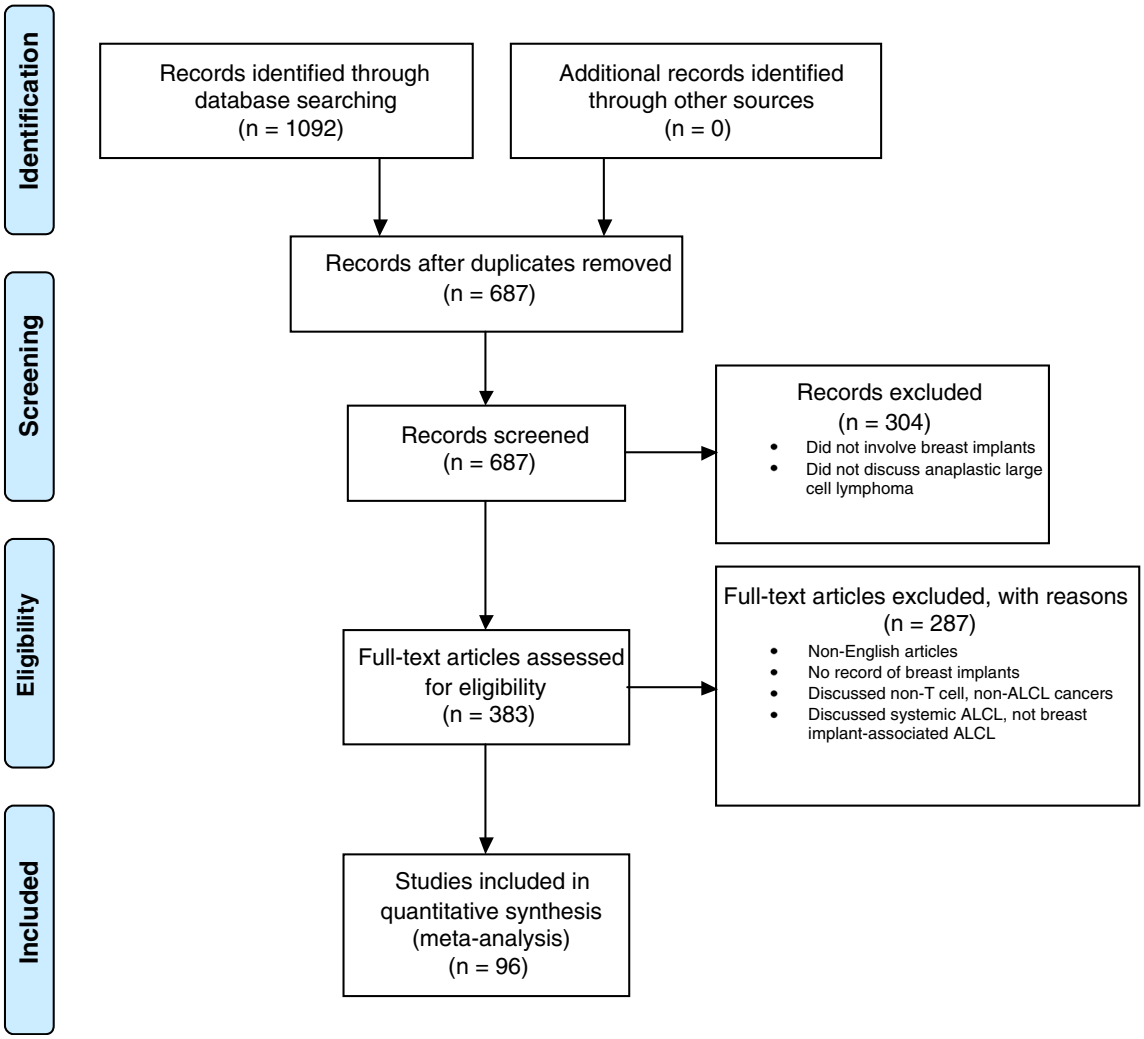

Fig. 1 PRISMA 2009 flow diagram for systematic review on BIA-ALCL

could develop in genetically predisposed individuals who are exposed breast implants [7, 22].

Diagnosis

The most common presentation of BIA-ALCL is delayed seroma seen more than 1 year after implantation. Patients who present later in their course may also have a mass [24•, 25]. The first step in diagnosis includes obtaining a fine needle aspiration of the seroma, which should be sent for cell block cytology, histology, CD30 immunohistochemistry, which is a lymphoma tumor marker, and anaplastic lymphoma kinase (ALK) [25–27]. The fluid collected may be serous, viscous, or bloody, which can confound the diagnosis of BIA-ALCL with infection; however, histology will demonstrate large pleomorphic cells with prominent horseshoe-shaped nuclei, and strong, diffuse, CD30 reactivity. BIA-ALCL is ALK negative, and ALK is associated with systemic ALCL [27].

Ultrasound is currently recommended for screening [26]. Mammography is discouraged as BIA-ALCL does not cause detectable microcalcifications [26]. Once the diagnosis of BIA-ALCL is confirmed, positive electron tomography (PET) and computed tomography (CT) scans should be obtained to stage the disease and aid in surgical planning. We also recommend consultation with medical oncology, especially in cases of advanced disease which may require chemotherapy or brentuximab [28, 29].

Treatment and Outcomes

BIA-ALCL is considered an indolent disease with an excellent prognosis when discovered in the early stages, such as IE (breast only) and IIE (breast and ipsilateral axillary lymph nodes) [26]. An important prognostic factor is the extent of disease at the time of diagnosis and treatment [9, 15••]. Miranda et al. found that complete remission was seen in 93% of patients when the disease was confined to the fibrous

Table 1 Breast implant–associated ALCL (1997–2019): clinical features of 91 patients

Clinical features	No.	%
Age (years)		
Mean	52.5	
Range	24–87	
Affected side		
Right	50	55
Left	34	37
Unknown	7	8
Reason for implant		
Cosmetic	47	52
Breast cancer	37	41
Unknown	7	7
Interval to lymphoma diagnosis (years)		
Mean	10.9	
Median	8	
Range	2–35	
Initial presenting symptom		
Seroma	62	68.1
Mass	3	3.3
Seroma + mass	12	13.2
Lymphadenopathy	13	14.3
Skin findings*	6	3.3
B symptoms	3	6.6
Unknown	5	5.5
Stage of disease at presentation		
I	61	67
II	12	13
III	3	3
IV	3	3
Unknown	12	13

*Skin findings: cutaneous nodules, erythema, or pruritus

Table 2 Treatment and outcomes of 91 patients with breast implant–associated anaplastic large cell lymphoma between 1997 and 2019

	No.	%
Treatment		
Surgery only	36	39.6
Surgery and chemotherapy	20	22.0
Surgery and radiation	4	4.4
Surgery, chemotherapy, and radiation	13	14.3
Surgery, chemotherapy, radiation, and stem cell transplant	3	3.3
Surgery, chemotherapy, and stem cell transplant	1	1.1
Chemotherapy only	4	4.4
Chemotherapy and radiation	2	2.2
Unknown	8	8.8
Patient outcomes		
Disease-free survival	64	70.3
Recurrence followed by DFS	3	3.3
Recurrence, then lost to follow-up	4	4.4
Death	5	5.5
Unknown	14	16.5

capsule, while only 72% of patients with a tumor mass at initial presentation had complete remission [15••]. The presence of a mass was statistically significant for worse overall survival and worse progression-free survival ($P = 0.052$ and $P = 0.03$) [15••]. Interestingly, having lymph node involvement demonstrated higher rates of complete remission (67%, $P = 0.128$) when compared with patients who had bilateral disease (57%, $P \leq 0.001$), suggesting more locally extensive disease was of higher risk than advanced disease [9].

Definitive surgery, which includes explantation, total capsulectomy, and tumor ablation, has demonstrated significant benefits. Collins et al. found that patients with more advanced disease had a longer time from diagnosis to surgery (21 vs 8 months, $P = 0.0039$) and a lower rate of definitive surgery (59% vs 88%, $P = 0.004$) [9]. This concept was further supported by Miranda's prospective cohort of 60 patients, 93% of whom were managed by definitive surgery, and had a mean overall survival of 12 years across all patients [15••]. A case series by Clemens et al. supported this claim by showing that patients who underwent complete surgical excision had better overall survival than patients who had incomplete surgical management including partial capsulectomy, systemic chemotherapy, or radiation therapy ($P = 0.022$ for overall survival, $P = 0.014$ for event-free survival) [30••]. For best outcomes, it is imperative that suspicious lymph nodes be excised and for a negative tumor margin to be obtained during surgery [15••, 24•, 30••, 31]. Also, to date, no patients who have died from BIA-ALCL underwent definitive surgery [9].

If there is systemic metastasis, adjuvant chemotherapy with anthracycline-based agents (such as a CHOP regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone) or brentuximab vedotin is used, along with stem cell transplant [9, 24•, 28, 29]. Even with metastatic disease, case reports show that surgery and chemotherapy can lead to a relatively favorable prognosis, with several patients with stage IV BIA-ALCL achieving disease-free status [24•].

Immediate reconstruction after treatment of BIA-ALCL is only advised for patients with surgically resectable, early-stage IA-IC disease. Autologous tissue reconstruction is considered the gold standard for breast cancer patients with significant contralateral breast ptosis or for those who desire a natural, implant-free reconstruction [32, 33]. In BIA-ALCL patients, both latissimus dorsi and bilateral deep inferior epigastric flaps have been utilized [24•]. Other secondary reconstructive options include reimplantation with non-textured implants, serial fat grafting, and mastopexy [24•]. Anything including and beyond stage IIA is best managed by repeating imaging 6–12

months after surgical resection, and assuring that there is no recurrence before planning for reconstruction [24•].

Discussion

Since the first reported case of BIA-ALCL, significant efforts have been made to understand the causal link between textured breast implants and ALCL, with the World Health Organization recognizing BIA-ALCL as a distinct subtype of lymphomas [11]. While improved recognition of the condition has aided in early detection of disease and appropriate interventions resulting in high rates of survival and patient satisfaction with subsequent reconstruction, the increased public awareness of the disease has been a source of unease for patients who already have implants, or those who are considering reconstructive or cosmetic procedures [24•].

For patients considering breast implants, whether it be for reconstruction after breast cancer or for cosmetic surgery, it is important that surgeons help patients make a shared and informed decision about implant-based breast surgery. Estimates based on breast cancer registries show that textured implants can be a risk for developing BIA-ALCL and it is between 1:1000 and 1:30,000 patients [4, 8•]. The wide range of risk estimates could be unsatisfactory for some, but this is mainly due to the small number of cases reported to date. Breast cancer registries are currently being established to better understand the epidemiology of the condition [34].

While the exact pathogenesis of the condition remains unclear, when advising patients, it is reasonable to explain that BIA-ALCL appears to be a disease with an indolent course and excellent prognosis when caught early. Mean overall survival may be as high as 12 years, with 93% survival at 3 years [15••]. The most significant risk for recurrence or death is the presence of a mass at the time of presentation, extracapsular disease extension, and incomplete resection. Patients should be advised that definitive surgical management is most beneficial [24•, 26]. For patients who have textured implants but are asymptomatic, the FDA discourages prophylactic removal and does not recommend routine follow-up of asymptomatic patients with implants [12, 13]. The American Society of Plastic Surgeons also discourages prophylactic implant removal because "the risks associated with surgery are greater than the risk of developing BIA-ALCL" [35].

Given a growing body of concern for patients regarding the risks of BIA-ALCL, careful consideration must be given for the expansion of alternatives to the use of breast implants. In breast reconstruction, the use of autologous reconstruction is often less preferred by patients for reasons such as cosmesis, downtime, donor site scarring, and fear of longer surgery times [36, 37]. However, as flap-based surgery becomes faster and smoother, consideration of use of these methods may expand as a result of concern for BIA-ALCL, particularly in cancer patients. For cosmetic patients, autologous large volume fat grafting has emerged as a useful technique for cosmetic breast enhancement [35]. Initial concern for the possible risk of cancers has largely been disproven and outcomes of breast enhancement with fat grafting have been excellent [35]. The consideration of autologous microvascular breast enhancement may also be an option for patients given the broad expertise that has developed across the country [36].

Breast reconstruction after surgical management of BIA-ALCL may be appropriate, as the recurrence rate after surgical resection is relatively low and estimated to be 4% after 5 years [30••]. Therefore, many patients are candidates for subsequent breast reconstruction. For patients with unilateral BIA-ALCL, the surgeon can consider removing the contralateral implant in the unaffected breast, as 4.6% of reported cases had bilateral disease [1, 2]. Once definitive surgery with explantation, capsulectomy, and tumor ablation is complete, patients may be considered for immediate or delayed reconstruction based on disease staging.

However, textured implants may be contraindicated in reconstruction, especially since to date, BIA-ALCL has been almost exclusively associated with textured implants. According to the FDA's statement in July 2019, there have been 573 cases of BIA-ALCL reported to the global Medical Device Reports [13]. Of those, 26 cases have been associated with smooth implants. However, 7 of these smooth implant cases have a history of having textured implants, and the remaining 19 cases had multiple revisions and an unclear history of types of implants previously used, suggesting that textured implants may have been used in these patients at some time in their history [12, 13]. There are two case reports that suggest BIA-ALCL may have occurred after using smooth implants, but the authors do not report enough data to evaluate the implant type (smooth vs textured) or the surgical history of these patients (i.e., may have smooth implants at the time of BIA-ALCL diagnosis but have had a history of textured implants) [34, 37]. In August 2019, in response to the increasing number of case reports, the FDA requested that Allergan voluntarily recall its Natrelle BIOCELL textured implant [12].

Understandably, successfully treated BIA-ALCL patients have heightened concerns for developing what they perceive as an iatrogenic malignancy, making a thorough conversation about treatment options essential. When Lamaris et al. surveyed 66 patients who underwent reconstruction after BIA-ALCL, 94% of patients who received various types of reconstruction including smooth implants, immediate mastopexy, autologous flaps, and fat grafting expressed satisfaction or high satisfaction with the reconstruction [24•]. The one patient who was unsatisfied had smooth implants placed, and it was revealed that while the patient was satisfied with the cosmetic result of the reconstruction, she regretted opting to have another implant placed, as she feared recurrence of the disease [24•]. This demonstrates that the anxiety experienced by

patients with breast implants may have a significantly negative effect on quality of life and treatment satisfaction, even when patients are disease free with excellent reconstructive results. Beyond overall survival, there is a need to further investigate the cost of the psychological effects of breast reconstruction after a perceived iatrogenic malignancy.

Recently, there was a report of a textured gluteal implant–associated ALCL, indicating that textured implants may trigger histologic disease in other areas of the body [25]. Once the pathogenesis of BIA-ALCL is better understood, our understanding of BIA-ALCL as an entity of a broader category of implant-associated ALCL may aid in advancements in prevention, diagnosis, and management.

Despite concerns over use of textured implants, implant-based reconstruction will remain a desirable option for patients seeking reconstructive breast surgery. As such, we must respond to new challenges facing the future of implant-based breast surgery. Capsular contracture, for example, is one of the most common complications associated with implant-based breast reconstruction with a reported incidence of up to 25% over a 10-year period [41]. The risk for capsular contracture was previously mitigated through use of textured implants as well as subpectoral implant placement [41–43]. As awareness of BIA-ALCL increases, however, the use of textured implants is likely to decrease, and a new importance will emerge for alternative strategies to decrease risk for capsular contracture. One such technique is through the use of acellular dermal matrices [44–46]. Salzberg et al. report a capsular contracture rate of 0.8% (average follow-up of 4.7 years) in patients undergoing ADM-assisted breast reconstruction [44], which is a significant reduction compared with the incidence reported in the core studies over the same time frame [47–57]. Recent studies examining the immunohistochemistry of breast capsules after implant-based reconstruction show a significantly reduced concentration of myofibroblasts in ADM reconstructed capsules compared with those reconstructed without use of ADM [44–46]. It is our hope that future studies will explore this relationship further.

Limitations

Our systematic review is primarily limited by the presence and quality of previously published literature or lack thereof. Further, due to the rarity of the condition, some case reports included data from patients that was already published, and we made the best efforts to avoid duplicates.

Conclusion

BIA-ALCL is a relatively new lymphoma almost exclusively associated with textured breast implants. Because of their use during reconstruction after mastectomy for breast cancer, breast cancer specialists are encouraged to be aware of diagnosis and treatment of this condition. While BIA-ALCL usually carries an excellent prognosis when managed appropriately, the perceived iatrogenic nature of the condition may place a high psychological burden on patients. Beyond surgical management and treatment outcomes, it is important for physicians to be aware of the nuances of the diagnosis to help patients make informed decisions for treatment and subsequent reconstruction. As the algorithm for breast cancer treatment is ever-changing, so, too, is the attempt to mitigate reconstructive complications and to improve aesthetic outcomes.

A continued dialogue on the pathogenesis and treatment of this condition is likely to have a broad impact on the future of breast reconstruction and implant-based breast surgery as a whole.

Compliance with Ethical Standard

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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