Giant juvenile fibroadenoma: a systematic review with diagnostic and treatment recommendations

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Background: Currently, there is a lack of clear guidelines regarding evaluation and management of giant juvenile fibroadenomas. The purpose of this study was to conduct a systematic review of giant juvenile fibroadenomas and to evaluate the most common diagnostic and therapeutic modalities.

Methods: A systematic literature search of PubMed and MEDLINE databases was conducted in February 2014 to identify articles related to giant juvenile fibroadenomas. Pooled outcomes are reported.

Results: Fifty-two articles (153 patients) met inclusion criteria. Mean age was 16.7 years old, with a mean lesion size of 11.2 cm. Most patients (86%) presented with a single breast mass. Imaging modalities included ultrasound in 72.5% and mammography in 26.1% of cases. Tissue diagnosis was obtained using a core needle biopsy in 18.3% of cases, fine-needle aspiration (FNA) in 25.5%, and excisional biopsy in 11.1% of patients. Surgical treatment was implemented in 98.7% of patients (mean time to treatment of 9.5 months, range, 3 days to 7 years). Surgical intervention included excision in all cases, of which four were mastectomies. Breast reconstruction was completed in 17.6% of cases. There were no postoperative complications.

Conclusions: Diagnosis and treatment of giant juvenile fibroadenoma is heterogeneous. There is a paucity of data to support observation and non-operative treatment. The most common diagnostic modalities include core needle or excisional biopsy. The mainstay of treatment is complete excision with an emphasis on preserving the developing breast parenchyma and nipple areolar complex. Breast reconstruction is uncommon, but may be necessary in certain cases.

Keywords: Fibroadenoma; juvenile; giant; breast; phyllodes; mastectomy

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Introduction

Fibroadenomas are the most common type of breast tumors diagnosed in young women. Fibroadenomas found in children and adolescents are termed juvenile fibroadenomas (1). A juvenile fibroadenoma is considered "giant" if it is greater than 5 cm, 500 grams, or replaces at least 80% of the breast (1). Giant juvenile fibroadenomas are less common than fibroadenomas and comprise 1-8% of breast lesions in the adolescent population (1,2). Management of juvenile fibroadenomas includes surgical resection or observation since complete tumor regression may occur in 10-59% of lesions (1,3). These benign tumors have a propensity for rapid growth resulting in discomfort, self-consciousness, and anxiety (4,5). This is known to result in unpleasant interactions with their peers and has a considerable impact on these patients' psychological and



Figure 1 PRISMA flow diagram of the search process and selection of included studies.

emotional state (4). Other conditions of the breast tissue may be mistaken for fibroadenomas including physiologic hypertrophy, phyllodes tumor, and inflammatory processes such as a breast abscess (6).

To date, there is a lack of specific guidelines regarding the optimal management of giant juvenile fibroadenomas likely due to conflicting diagnostic and treatment strategies, variation in patient age and the degree of breast development, and differences in patient preferences (7). The purpose of this study was to systematically review the available literature pertaining to giant juvenile fibroadenomas, to report data pertaining to the patient population and their clinical presentation, and to evaluate diagnostic and treatment strategies.

Materials and methods

An electronic search of the MEDLINE and PubMed databases was conducted according to PRISM criteria to identify articles published between January 1946 and February 2014 (*Figure 1*) (8). Search terms included 'fibroadenoma', 'giant', 'adolescent' using controlled vocabulary (MeSH terms). Inclusion criteria included case reports and case series of giant juvenile fibroadenomas, written in English. Titles were reviewed by a single author (M.P) for candidacy of abstract review. Abstracts were then reviewed for full text article review. The bibliographies of all manuscripts were reviewed

to identify additional references that were not captured in the initial search. Exclusion criteria included manuscripts focused on cytology/molecular analysis, those lacking clinical subjects, and those focused on non-giant juvenile fibroadenomas, animal studies, and review articles.

Data was then extracted from each manuscript to capture: patient age, comorbidities, tumor size (reported as largest dimension), presence of a single or multiple tumors, location, unilateral or bilateral, pain at presentation, time to intervention, diagnostic modality, treatment (observation, medical, or surgical), surgical complications, patient outcomes, time of follow-up, and whether patients underwent reconstructive surgery. The complete demographic and clinical data of the included studies are reported in *Table 1*.

Results

A total of 52 articles (47 case reports and 5 case series) met inclusion criteria and were included for review (*Table 2*). These articles encompassed a total of 153 patients with a mean age of 16.7±4.1 years (range, 9-25 years). Fifty percent of the articles (26/52), which included 103 patients, were published in the last ten years. Fibroadenoma size ranged from 3 to 60 cm with a mean of 11.2±9.09 cm. Eighty-six percent of cases (4,5,10,11,16,18,19,25,27,29,30,32-34, 40-42,44-46,49,50,52,54) presented as a solitary mass (n=131) (9,13,14,19-21,23,26,38,47,53,55-57), while 14.4% presented

Author	Type of reconstruction	Uni-/bilateral	Uni-/bilateral	Tumor	Immediate/
Author, year	Type of reconstruction	disease	reconstruction	size (cm)	delayed
Park et al. 2006 (9)	Five mammopexy, two reduction mammoplasty	Unilateral	Unilateral	-	-
Chepla <i>et al</i> . 2011 (10)	Dermoglandular preserving mastopexy	Unilateral	Unilateral	15	Immediate
Ng et al. 2011 (11)	Breast reduction	Unilateral	Unilateral	19	Immediate
Poh et al. 2010 (12)	Adjustable implant	Bilateral	Bilateral	12	Delayed
Wolfram <i>et al</i> . 2009 (13)	Correction of breast asymmetry	Unilateral	Unilateral	-	Delayed
Dolmans et al. 2007 (14)	Contralateral augmentation	Unilateral	Unilateral	9	Immediate
Lee et al. 2004 (15)	Central pedicle reduction mammoplasty with	Bilateral	Bilateral	17	Immediate
	transposed nipple-areola				
Wechselberger et al.	Reduction mammoplasty	Unilateral	Unilateral	-	Immediate
2002 (16)					
Musio <i>et al</i> . 1991 (17)	Subpectoral implants with nipple reimplantment	Bilateral	Bilateral	16	-
Uygur <i>et al</i> . 2009 (18)	Nipple as graft, reshaped breast tissue	Unilateral	Unilateral	22	Immediate
Merdan <i>et al</i> . 2006 (19)	Unknown type	Unilateral	Unilateral	13	Immediate
Robbins <i>et al</i> . 1979 (20)	Nipple-bearing dermal pedicle	Unilateral	Unilateral	11	Immediate
Hoffman <i>et al</i> . 1978 (21)	Skin graft & silicone implants	Unilateral	Unilateral	-	Immediate
Kuusk e <i>t al</i> . 1988 (22)	Implantation of subpectoral tissue expander	Unilateral	Unilateral	3.5	-
Kamei et al. 2000 (23)	Tissue expander for 4mo, no definitive recon	Unilateral	Unilateral	10	Immediate
Schneider et al. 1997 (24)	Tissue expander	Unilateral	Unilateral	6.5	-
Ağaoğlu <i>et al</i> . 2000 (25)	Mastectomy with subpectoral silicone implant	Unilateral	Unilateral	-	Immediate
Cerrato et al. 2015 (26)	One breast reshaping with wise pattern reduction	Unilateral	Unilateral	7.4	Immediate
	technique, one saline implant				

Table 1 Studies involving patients who received surgical reconstruction

Table 2 Included studies

Author	Voar	Country	n	٨٩٥	Size	Multiple/	Uni/bilateral	Pain	Days before	Reconstruction	Co-morbidities
	Tear			Aye	(cm)	single			intervention		
Ezer (27)	2013	Turkey	4	14	25	Single	Unilateral	-	60	Ν	Ν
				17	30	Single	Unilateral	_	180	Ν	Ν
				10	45	Single	Unilateral	_	3	Ν	Neuroblastoma
				14	60	Single	Unilateral	_	10	Ν	Ν
Matz (28)	2013	US	1	13	10	Multiple	Unilateral	Yes	-	Ν	Ν
Arowolo (29)	2013	Nigeria	1	14	30	Single	Unilateral	Yes	365	Y	Ν
Biswas (30)	2012	Bangladesh	2	14	15	Single	Unilateral	Yes	120	Ν	Ν
				16	11	Single	Unilateral	No	90	Ν	Ν
Sosin (31)	2012	US	1	13	12.1	Multiple	Unilateral	_	-	Ν	Ν
Cheng (32)	2012	US	3	17	5	Single	Unilateral	No	30	Ν	ESRD, post-transplant
				13	8	Single	Unilateral	No	210	Ν	Ν
				15	10.5	Single	Unilateral	No	90	Ν	Ν
Heilmann (33)	2012	Germany	1	17	13	Single	Unilateral	No	60	Ν	Pregnancy
Izadpanah (34)	2012	Canada	1	12	9.5	Single	Unilateral	Yes	8	Ν	Ν
Marshall (35)	2012	US	1	15	3.3	Multiple	Unilateral	Yes	270	Ν	Ν

Table 2 (continued)

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Table 2 (continued)

Author	Year	Country	n	Age	Size	Multiple/	Uni/bilateral	Pain	Days before	Reconstruction	Co-morbidities	
Chepla (10)	2011	US	2	10	11.6	Single	Unilateral	_	60	N	N	
onopia (10)	2011	00	-	16	15	Single	Unilateral	No	730	Y	N	
Na (11)	2011	Canada	1	17	19	Single	Unilateral	_	_	Y	N	
Nikumbh (36)	2011	India	1	12	17	Multiple	Bilateral	Yes	90	N	N	
Tantridge (37)	2011	UK	1	13	11.2	Multiple	Bilateral	No	60	N	Hemihypertrophy of	
Yagnik (38)	2011	India	1	15	13	Single	Unilateral	_	240	Ν	N	
McCague (39)	2010	US	1	22	28	Multiple	Bilateral	Yes	2555	Y	Ν	
Poh (12)	2010	US	1	12	12	Multiple	Bilateral	No	150	Y	Beckmann-Wiedemann syndrome	
Biggers (40)	2009	US	4	11	5.9	Single	Unilateral	_	90	Ν	N	
				12	10.5	Single	Unilateral	_	90	Ν	Ν	
				14	12	Single	Unilateral	_	90	Ν	Ν	
				15	17	Single	Unilateral	_	90	Ν	Ν	
Calcaterra (41)	2009	Italy	1	12	17	Single	Unilateral	No	-	Ν	Turner syndrome	
Gobbi (42)	2009	Italy	2	12	8	Single	Unilateral	No	-	Ν	Ν	
				15	10	Single	Unilateral	No	60	Ν	Ν	
Uygur (18)	2009	Turkey	1	18	22	Single	Unilateral	No	-	Y	Ν	
Mukhopadhyay (2)	2009	India	1	11	22	Multiple	Bilateral	Yes	60	N	Ν	
Wolfram (13)	2009	Austria	1	15	_	Single	Unilateral	No	90	Y	Severe scoliosis	
Dolmans (14)	2007	Netherlands	1	18	9	Single	Unilateral	No	_	Y	Ν	
Moore (43)	2007	US	1	9	18.5	Multiple	Bilateral	-	365	Ν	Congenital tubular breast disorder	
Merdan (19)	2006	Iraq	1	14	13	Single	Unilateral	No	300	Y	Ν	
Ahuja (44)	2005	India	1	12	-	Single	Unilateral	No	60	Ν	Ν	
Lee (15)	2004	South Korea	1	11	17	Multiple	Bilateral	No	365	Y	Ν	
Daya (45)	2003	South Africa	2	16	18	Single	Unilateral	Yes	730	N	Ν	
				15	15	Single	Unilateral	-	365	Ν	Ν	
Zacharia (46)	2003	India	1	13	8	Single	Unilateral	-	30	Ν	-	
Hanna (47)	2002	Kuwait	11	15	6	Multiple	Bilateral	No	365	Ν	Ν	
				21	15	Single	Unilateral	No	-	Ν	Ν	
				21	15	Single	Unilateral	No	-	Ν	Pregnancy	
				20	10	Single	Unilateral	No	-	Ν	Ν	
				20	13	Single	Unilateral	No	-	Ν	Ν	
				25	17	Single	Unilateral	No	-	Ν	Ν	
				25	10	Single	Unilateral	No	-	Ν	Ν	
				25	10	Single	Unilateral	No	2190	Ν	Ν	
				23	15	Single	Unilateral	No	180	Ν	Ν	
				25	8	Single	Unilateral	Yes	-	Ν	Ν	
				25	6	Single	Unilateral	Yes	180	Ν	Ν	
Wechselberger (16)	2002	Austria	1	15	-	Single	Unilateral	No	365	Y	Ν	

 Table 2 (continued)

 Table 2 (continued)

Author	Year	Country	n	Age	Size (cm)	Multiple/ single	Uni/bilateral	Pain	Days before intervention	Reconstruction	Co-morbidities
Davis (4)	2001	US	1	19	5	Single	Unilateral	No	7	Ν	Androgen Insensitivity
											Syndrome
Agaoglu (25)	2000	Turkey	1	16	-	Single	Unilateral	Yes	180	Y	Ν
Baxi (48)	2000	India	1	16	8	Multiple	Bilateral	No	730	Ν	Ν
Kamei (23)	2000	Japan	2	19	11	Single	Unilateral	-	_	Y	Ν
				17	10	Single	Unilateral	-	_	Y	Ν
Mashiloane (49)	2000	South Africa	1	16	-	Single	Unilateral	Yes	170	Ν	Pregnancy
Simmons (50)	2000	US	1	12	14	Single	Unilateral	No	90	Ν	Ν
Silfen (51)	1999	South Africa	1	13	_	Multiple	Bilateral	Yes	365	Ν	Ν
Schneider (24)	1997	Germany	1	25	6.5	Multiple	Unilateral	No	180	Ν	Ν
Guerin (52)	1993	France	1	14	16	Single	Unilateral	Yes	390	Ν	Ν
Amiel (5)	1993	France	1	15	13	Single	Unilateral	No	-	Ν	Ν
Musio (17)	1991	US	1	18	16	Multiple	Bilateral	No	600	Y	Pregnancy
Kuusk (22)	1988	Canada	1	14	3.5	Multiple	Unilateral	-	120	Y	Ν
Leis (53)	1982	US	1	11	8	Single	Unilateral	-	240	Ν	Ν
Robbins (20)	1979	Australia	1	20	11	Single	Unilateral	-	_	Y	Ν
Hoffman (21)	1978	US	1	13	_	Single	Unilateral	-	120	Y	Ν
Devitt (54)	1974	Canada	2	14	12	Single	Unilateral	Yes	150	Ν	Ν
				19	_	Single	Unilateral	No	548	Ν	Ν
Cerrato (26)	2015	US	46	18	7.4	Single	Unilateral	No	-	Y	Ν
Ugburo (55)	2012	Nigeria	16	14	_	Single	Unilateral	No	204	Ν	Ν
Park (9)	2006	US	9	18	_	Single	Unilateral	_	-	Y	Ν
Sönmez (56)	2006	Belgium	2	_	7	Single	Unilateral	No	210	Ν	Ν
Abdelhadi (57)	2005	Saudi Arabia	9	21	14	Single	Unilateral	No	195	Ν	Ν

with multiple masses (n=22) (2,12,15,17,22,24,28,31, 35-37,39,43,47,48,51). Most cases (91.5%, n=140) presented as unilateral, while 8.5% (n=13) presented as bilateral. Follow-up time was recorded in 79.7% of patients (n=122). Mean follow-up was 14.7±18.8 months (range, 1 week to 84 months).

Pain was reported in 10.5% of cases (n=16). Imaging varied considerably with 72.5% of cases (n=111) having an ultrasound and 26.1% of cases (n=40) undergoing mammography. Of the patients who had a mammogram, 67.5% were cases that were published in the last 10 years. Tissue acquisition method included core needle biopsy in 18.3% (n=28), excisional biopsy in 11.1% (n=17), and fine-needle aspiration (FNA) in 25.5% (n=39) for cytological evaluation. Initial therapy included surgery in 98.7% of patients (n=151) and medical therapy in 1.3% (n=2). One patient received a gonadotropin-releasing hormone analog

and medroxyprogesterone acetate, but the minimal clinical response ultimately led to surgery (51). A second patient was thought to have a breast mass as a result of an inflammatory process and was given antibiotics. A minimal response also led to surgical excision (42). Mean time to treatment was 9.5 months (range, 3 days to 7 years). Surgical intervention included mass excision in all cases with the exception of four patients (12,14,24,25) that required total mastectomy. Breast reconstruction was completed in 17.6% of cases (n=27). The type of breast reconstruction is detailed in Table 1. Most patients (92.2%) were in excellent health (n=141), while 5.2% (n=8) of patients had a pre-existing condition, including neuroblastoma (n=1) (27), (end stage renal disease) status post post-kidney transplant (n=1) (32), generalized body hemihypertrophy of unknown etiology (n=1) (37), Beckwith-Wiedemann syndrome (n=1) (12), Turner syndrome (n=1) (41), severe scoliosis (n=1) (13),

congenital tubular breast disorder (n=1) (15), and androgen insensitivity syndrome (n=1) (4). Four patients (2.6%) were pregnant at the time of presentation (17,33,47,49). On final pathology, no specimen demonstrated malignancy. There were no reported post-operative complications. Fibroadenomas recurred in 3.9% of cases (n=6), requiring re-excision. Two patients demonstrated recurrence twice and the timing of recurrence ranged from 2 months to 4 years (9,22,37,41,51).

Discussion

Giant juvenile fibroadenomas, composed of epithelium and/ or stroma of the terminal lobule of the breast, represent only 0.5% of all fibroadenomas (9,41). Fibroadenomas typically present as unilateral firm nontender masses that may enlarge with relation to the menstrual cycle (7). The term juvenile is a misnomer since giant fibroadenomas have been found in children as young as 9 years old and as old as 25 years old. In fact, a juvenile fibroadenoma has been reported in an infant as young as 3 weeks old (58).

Currently, there is a lack of clear guidelines regarding diagnostic and treatment modalities, and management varies among breast surgeons, obstetricians/gynecologists, pediatricians, and pediatric surgeons, all of whom may encounter a patient with a giant juvenile fibroadenoma. Referral to a specialist with experience in the management of such patients should facilitate a more focused evaluation and treatment strategy. The purpose of this literature review was to develop an evidence-based consensus regarding diagnosis and treatment by evaluating all reported cases of juvenile giant fibroadenomas. To our knowledge, this is the largest and most current clinical review of giant juvenile fibroadenomas.

Historically, fibroadenomas have been described as painless masses (59,60), yet 10% of the patients in our review reported pain. Over one third of the patients in this review underwent mammography in conjunction with another diagnostic modality, usually ultrasonography. The use of mammograms in young females has widely been documented to be of limited value due to increased breast density (60,61). The utility of mammography for a suspected giant juvenile fibroadenoma is limited due to poor image quality in younger patients as well as the extremely low risk of malignancy (42,57). Ultrasonography is the most common method of evaluation as demonstrated with this review. Smith *et al.* (62) found that patients aged 25 and younger suspected to have a fibroadenoma on ultrasound had 78.8% accuracy in diagnosis based on histology. However, amongst the same cohort of patients, ultrasonography proved to be a superior diagnostic negative predictive value for malignancy of 99.5% (42). Within that study, larger lesions, (3 cm or larger) and recurrent lesions were more likely to be diagnosed as phyllodes tumor or malignancy supporting the need to obtain tissue for diagnosis with large lesions. While FNA was used in over one third of the patients reported in this review, FNA may not reliably differentiate between a fibroadenoma and phyllodes tumor (11). In fact, one of the largest series of over 1,400 FNAs of adolescent breast masses, Kapila et al. concluded FNA is not required (63). The lack of an ideal diagnostic tool, coupled with the potential for rapid tumor growth makes complete surgical excision an excellent diagnostic and treatment modality. The safety profile of total excision is remarkable without reports of postoperative complications and a low recurrence rate of tumor.

Emphasis on preserving the developing breast parenchyma and nipple areolar complex is of paramount importance in achieving superior aesthetic results (61). Giant juvenile fibroadenomas may compress normal breast tissue, which may falsely minimize the perception of nondiseased parenchyma. However, the remaining displaced breast tissue will often fill in the void left by the excised giant juvenile fibroadenoma, precluding the need for reconstruction (31).

This systematic review did not disclose any malignancy or phyllodes tumor on final pathology. This may be due to the retrospective nature of this study. Most medical and surgical publications usually describe any giant mass in terms of the pathological disease on final pathology that would likely be missed on a database search. We address this limitation because of its importance in selecting proper diagnostic modalities during the fibroadenoma work-up.

According to the Surveillance, Epidemiology, and End Results (SEER) program maintained by the National Cancer Institute, the age-adjusted incidence of all malignant pediatric breast tumors in 2003 was 0.08 cases per 100,000 people and a total of 75 malignant breast tumors were identified over a 40-year interval (64). Because phyllodes tumors present in similar fashion and share histological similarities with fibroadenomas, surgeons may feel compelled to rule out malignant phyllodes tumor with a core needle biopsy as intervention would require wider excisional margins. However, the incidence of malignant phyllodes tumor is incredibly rare. Some of the largest reviews and case series describe 19 total cases reports in

the literature up to 1994 (65), 5 cases between 1982 and 1996 (66), and 29 cases identified between 1973 and 2004 (64). Most childhood phyllodes tumors are benign (rarely borderline) and surgical intervention need not differ from simple excision (67-71). Based on the available phyllodes tumor data and this giant juvenile fibroadenoma review, it is reasonable to progress toward excisional biopsy in obtaining tissue for definitive diagnosis and as a form of intervention. Additionally, in our experience pediatric patients do not tolerate core needle biopsies well and the procedure may negatively impact the adolescent patient both psychologically and emotionally more than the adult patient. In the event that a patient defers excisional biopsy, tissue diagnosis using core needle biopsy (with/without ultrasound guidance or stereotactic techniques depending on lesion location) is appropriate. Furthermore, multiple conditions may predispose a young patient to malignant phyllodes tumor such as, childhood osteosarcoma (72), Hodgkins lymphoma (73), neurofibromatosis (74), and other genetic mutations prone to malignancy (Li Fraumeni spectrum syndromes, p53 mutation, BRCA1, BRCA2, etc.) (75). Core needle biopsy may be indicated in this high risk cohort.

Mastectomy as a treatment modality for giant fibroadenomas has been debated but is commonly reserved for unusual or recurrent cases (9). For the rare case requiring mastectomy as the initial form of excision, patients are likely to undergo reconstructive surgery. The majority of the patients who received breast reconstruction underwent immediate reconstruction, the advantages of which include limiting the treatment to a single surgical procedure and avoiding the psychosocial consequences of a breast deformity (9). However, the disadvantages of immediate reconstruction are two-fold, and include a compromised aesthetic result when the surgeon is unable to address minor revisions and when the surgeon is unable to achieve breast symmetry. Chang et al. (6) advocate for reconstruction according to three basic principles: "preserving all the normal breast parenchyma, adjusting the skin envelope, and positioning the nipple-areola complex for symmetry with the opposite breast." The use of prosthetic implants in reconstruction, local dermoglandular rearrangement, reduction mammaplasty techniques, and nipple grafting have all demonstrated positive outcomes (9,10,12,15,25).

To date this is the largest and most comprehensive review of giant juvenile fibroadenoma, but there are limitations to the study. The major confounder to this systematic review is that only level four and five evidence (case reports and case series) are included that contribute to publication bias. These publications are often unique and include patients with large, unusual, or bilateral tumors. The incidence of patients with smaller tumors or tumors that did not warrant surgical treatment was less likely to be captured in our literature review. The lack of any postoperative complications is unusual but may be related to the youth and excellent health of the majority of patients. The option of observation as a management strategy is poorly described in the literature. However, the mean time to surgery was 9.5 months elucidating an increased likelihood of failed observation in most cases.

In summary and based on this systematic review, the authors recommend ultrasonography for lesion assessment and strongly encourage obtaining confirmatory tissue biopsy for histological evaluation. Tissue should be obtained based on patient-provider counseling and potential treatment strategy. If observation is recommended, a core needle biopsy should be considered (with/without ultrasonographic guidance or stereotactic guidance depending on the lesion location) to rule out malignancy. If surgical intervention is recommended (i.e., excision of lesion or mastectomy), a core needle biopsy or other invasive testing outside of the surgery should be avoided. There is little data to support the utility of mammography or FNA when evaluating a mass suspected to be a giant juvenile fibroadenoma.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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