

## ICMJE DISCLOSURE FORM

Date: 2021-3-4

Your Name: Shuo Li

Manuscript Title: Contralateral axillary lymph node metastasis and molecular changes in second primary breast cancer: a case report

Manuscript number (if known): \_\_\_\_\_ GS-21-137 \_\_\_\_\_

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## ICMJE DISCLOSURE FORM

Date: 2021-3-4

Your Name: Fei Xie

Manuscript Title: Contralateral axillary lymph node metastasis and molecular changes in second primary breast cancer: a case report

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Your Name: Yan Li

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1 **Case Report**

2

3 **Contralateral axillary lymph node metastasis and molecular changes in second**  
4 **primary breast cancer: a case report**

5

6 Shuo Li<sup>1#</sup>, Fei Xie<sup>2#</sup>, Yan Li<sup>1</sup>, Jue Wang<sup>1</sup>, Rui Chen<sup>1</sup>, Qian-Nan Zhu<sup>1</sup>, Xiao-Ming Zha<sup>1</sup>

7 <sup>1</sup>Breast Disease Department, the First Affiliated Hospital of Nanjing Medical

8 University, Nanjing, China; <sup>2</sup>Breast Disease Department, Third Affiliated Hospital of

9 Soochow University, Suzhou, China

10

11 <sup>#</sup>These authors contributed equally to this work.

12

13 Correspondence to: Prof. Xiao-Ming Zha. Breast Disease Department, the First

14 Affiliated Hospital of Nanjing Medical University, Nanjing, China. Email:

15 njzhaxm@njmu.edu.cn.

16

17 Li et al. Contralateral axillary lymph node metastasis in breast cancer

18

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23

24 **Abstract:** Contralateral axillary metastasis (CAM) is rather rare in primary breast

25 cancer. In this case, we present a 46-year-old female patient who underwent left breast-

26 conserving surgery (BCS) and left axillary lymph node dissection (ALND). Two years

27 later, an enlarged lymph node was found in her right axilla. Magnetic resonance

28 imaging (MRI) of the breast displayed a left breast mass with multiple internal

29 mammary lymph nodes and abnormal lymph nodes in the right axillary region.

30 However, no abnormalities were found in the right breast. The left breast mass was

31 diagnosed as invasive carcinoma by core needle biopsy. During the operation, we

32 suggested that the contralateral lymph nodes were metastatic from the second primary

33 breast cancer by preoperative <sup>99m</sup>Tc injection around the left breast. The patient

34 underwent left mastectomy and right axillary lymph node dissection. The postoperative

35 pathology was diagnosed as metachronous secondary primary left breast cancer, in  
36 which the initial presentation was lymph node metastasis to the contralateral axilla of  
37 the left breast. Therefore, we propose that CAM may be more common in second  
38 primary or recurrent breast cancer. It should be treated as locoregional extension.  
39 Preoperative lymph node markers are important to identify whether contralateral  
40 axillary lymph node metastasis occurs from a second primary breast cancer.

41 **Keywords:** Contralateral axillary node metastasis; breast cancer; preoperative lymph  
42 node markers; locoregional diffusion; case report

43

44

45

## 46 **#Introduction**

47

48 An important prognostic feature of breast cancer is lymph node metastasis, and it has  
49 reference significance for treatment options. In a study of sentinel lymph node drainage  
50 patterns in untreated breast cancer patients, breast lymphatic drainage was as follows:  
51 ipsilateral axilla (92.3%), intramammary (21.1%), interpectoral (2.1%), subclavian  
52 (2.6%), and supraclavicular (0.4%) (1). Contralateral axillary metastasis (CAM) is  
53 uncommon in primary breast cancer, and the reported incidence is between 3.5% and  
54 6%. CAM can occur with primary breast cancer either synchronously or  
55 metachronously and can be the only site of metastasis. The management of these  
56 patients, especially those without distant metastasis, is controversial (2). The reported  
57 literature has considered CAM as stage IV disease, and there are no standard guidelines  
58 for CAM.

59 We present a case of a 46-year-old female who was diagnosed with metachronous  
60 secondary primary breast cancer with CAM, which is extremely rare. The histopathology  
61 and tumor characteristics of the metachronous secondary primary breast cancer with CAM in  
62 this case is that the tumor is multifocal invasive carcinoma with focal poorly  
63 differentiated neuroendocrine carcinoma. IHC demonstrated that the left breast cancer  
64 was negative for ER, PR, and HER2, which was similar to the right metastatic axillary  
65 lymph nodes. We will describe how we confirmed the CAM of secondary primary  
66 breast cancer, along with our diagnosis, treatment, and follow-up.

67 We present the following article in accordance with the CARE reporting checklist.

## 68 **#Case presentation**

69

70 In 2016, a 44-year-old female patient presented to the outpatient department of The  
71 First Affiliated Hospital of Nanjing Medical University (Jiangsu, China) due to a left  
72 breast lump. Physical examination revealed a painless, hard, and poorly mobile mass in  
73 the upper inner quadrant of the left breast, 2.0 cm × 2.0 cm in size, without hydro derma,  
74 skin dimpling, nipple retraction, or nipple discharge. An ultrasound (US) displayed an  
75 irregularly shaped, lobulated, and calcified hypoechoic mass of 2.0 cm × 1.2 cm  
76 without abnormal axillary lymph nodes, which was classified as category 5 based on  
77 the Breast Imaging Reporting and Data System (BI-RADS) (3). A molybdenum  
78 mammogram revealed a patchy, irregular, and slightly high-density mass with  
79 heterogeneous cluster calcification, 1.0 cm × 1.8 cm in size. Core needle biopsy under  
80 ultrasonic guidance confirmed invasive carcinoma. After communicating with the  
81 patient about disease and surgical-related risks, she underwent left breast-conserving  
82 surgery (BCS) and left SLND. Intraoperative frozen pathology showed 1 of 4 lymph  
83 node metastases. She was suggested to undergo ALND. Postoperatively, histopathology  
84 revealed that the pathological diagnosis was invasive ductal carcinoma, with 1 of 10  
85 lymph node metastases. Immunohistochemistry (IHC) was positive for estrogen  
86 receptor (ER) and progesterone receptor (PR) but negative for human epidermal growth  
87 factor receptor 2 (HER2). In postoperative adjuvant therapy, she was treated with 4  
88 cycles of epirubicin (75 mg/m<sup>2</sup>) and cyclophosphamide (600 mg/m<sup>2</sup>) followed by 4  
89 cycles of paclitaxel (75 mg/m<sup>2</sup>), and then underwent radiation therapy to the chest wall.  
90 Following the completion of chemotherapy, the patient has taken tamoxifen orally until  
91 now. Since the operation, she has been subsequently followed up every 6 months.

92 Two years later, in 2018, this patient came to our clinic for complaints of enlarged  
93 right axillary lymph nodes. MRI of the breast revealed left breast cancer with multiple  
94 intra-breast metastases involving the nipple, areola, and skin, along with subcutaneous  
95 cancerous lymphangitis, numerous internal mammary lymph node metastases, and 1  
96 right axillary lymph node metastasis (Figure 1A, B). A 2.8 cm × 2.7 cm irregularly  
97 shaped and mixed echo mass in the upper quadrant of the left breast and a 1.8 cm ×  
98 1.0 cm enlarged lymph node in the right axillary region were displayed on US (Figure  
99 2A,B). Physical examination revealed a posterior nipple mass in the left breast and right  
100 axillary lymph node enlargement. No abnormalities were found in the right breast.  
101 Other primary sites or any distant recurrences were not detected by systemic

102 radiological examinations (brain MRI, chest CT, abdominal US, bone scintigraphy).  
103 The left breast mass was diagnosed as invasive carcinoma by core needle biopsy (Figure  
104 3).

105 After consultation with the multidisciplinary team (MDT), which consisted of  
106 pathologists, oncologists, and Radiologists, the patient underwent left mastectomy and  
107 right axillary lymph node dissection. To confirm whether right axillary lymph node  
108 metastasis occurred from the left breast or right occult primary cancer, we used <sup>99m</sup>Tc  
109 injected around the left breast mass and methylene blue next to the right areola prior to  
110 surgery. During the operation, the right axillary lymph nodes were found with both  
111 <sup>99m</sup>Tc and methylene blue, verifying that the right enlarged axillary lymph nodes were  
112 metastatic from the left breast. Pathology demonstrated multifocal infiltrating  
113 carcinoma in the left breast, with focal low differentiation neuroendocrine carcinoma  
114 involving the 4 quadrants and both vessels and nerves, and the largest quadrant had a  
115 maximum diameter of 5 cm. Four of 23 right-sided axillary lymph nodes showed  
116 metastatic carcinoma. IHC demonstrated that the left breast cancer was negative for ER,  
117 PR, and HER2, which was similar to the right metastatic axillary lymph nodes. They  
118 were all different from the previous breast cancer on the left side. Therefore, we  
119 considered that this was the main site of right axillary lymph node metastases and  
120 diagnosed metachronous secondary primary cancer, in which the initial presentation  
121 was lymph node metastasis to the contralateral axilla of the left breast. The patient  
122 received 6 treatments of paclitaxel liposomes and capecitabine followed by radiation  
123 therapy to the right axilla. Follow-up surveillance imaging included MRI of the breast  
124 as well as systemic radiological examination. She remains disease-free at 20 months  
125 post-operation.

126 Informed consent was taken from all the patients

127

## 128 **#Discussion**

129

130 CAM is quite uncommon in the absence of metastatic disease elsewhere. Three possible  
131 sources should be considered: contralateral spread from the primary breast cancer;  
132 metastasis from an occult primary in the contralateral breast; and metastasis from an  
133 extramammary site. CAM may be more common in second primary and recurrent breast  
134 cancers as obstruction or damage of conventional axillary lymphatics may cause  
135 collateral circulation. This blockage may be caused by surgery and radiotherapy. In a

136 meta-analysis of SLN biopsies in locally recurrent breast cancer by Maaskant-Braat et  
137 al., it was found that 43.2% of patients had abnormal drainage (4). Therefore, in second  
138 primary or recurrent breast cancer, the location of the sentinel lymph node becomes  
139 unforeseeable, confirming that after radiotherapy or previous surgery these drainage  
140 route changes may be obvious (5). In this case, the patient had previous left axillary  
141 lymph node dissection and radiotherapy. We hypothesized that CAM is caused by  
142 changes in lymphatic drainage and abnormal pathways and is secondary to lymphatic  
143 rather than blood-borne spread. Clinically, it is difficult to estimate CAM due to the  
144 lack of MRI to diagnose concealed contralateral tumors or failure to obtain adequate  
145 follow-up. However, CAM can be detected on preoperative lymphoscintigraphy and  
146 can be confirmed by lymph node biopsy and pathological diagnosis (6). IHC markers  
147 have been proven to usefully distinguish metastatic axillary lymph nodes from occult  
148 contralateral tumors. Here, we introduced a patient suffering from second primary left  
149 breast cancer and contralateral axillary lymph node metastasis. We confirmed this  
150 diagnosis by <sup>99m</sup>Tc and methylene blue, along with pathological IHC analysis. The  
151 IHC of the right lymph node was the same as that of the second breast cancer on the  
152 left, which was different from the primary tumor on the left.

153 It is rare if CAM has not metastasized to other distant organs, therefore, it is  
154 currently considered as M1 (stage IV) disease. Its management is considered  
155 complicated and is controversial. Nevertheless, some studies have reported that patients  
156 who develop CAM without other metastases to distant organs show longer overall  
157 disease-free survival than that of stage IV patients, which suggests that CAM should  
158 also be categorized as a local-regional disease (7). Therefore, treatment should intend  
159 to be curative rather than palliative. Moosdorff et al. performed a systematic review of  
160 CAM cases and reported an overall survival of 82.6% after an average follow-up of  
161 50.3 months. CAM compares more favorably than concurrent stage IV disease (8).  
162 Chkheidze et al. retrospectively analyzed the medical records of 12 patients diagnosed  
163 with breast cancer and CAM, which, however, gives no evidence of any other distant  
164 metastases reflected by their clinical features, pathologic diagnoses, therapy, and data  
165 of follow-up. They suggested that isolated CAM without distant organ metastasis  
166 represents regional diffusion rather than distant metastasis (9). There have been other  
167 similar cases of CAM reported. Kinoshita et al. reported a 64-year-old female with  
168 metachronous second primary left occult breast cancer initially presenting as right  
169 axillary lymph node metastases who had received breast-conserving therapy for left

170 breast cancer 4.5 years prior (10,11). Christina et al. presented a patient who was  
171 diagnosed with invasive ductal carcinoma after left BCS and ALND at 9 year follow-  
172 up (12). Gingerich et al. showed that an 81-year-old woman, suffering from apparent  
173 second primary breast cancer, had a history of invasive ductal breast cancer 18 years  
174 before CAM (13). All 3 of these patients underwent radiation therapy and initial ALND,  
175 and contralateral axillary lymph node involvement did not show significant clinical  
176 signs until second primary ipsilateral breast carcinoma was found. However, they did  
177 not confirm that the metastatic lymph nodes were from primary breast lesions. Kim et  
178 al. found through preoperative FDG PET/CT and lymphoscintigraphy that the patient  
179 had second primary breast cancer, which was accompanied by contralateral axillary  
180 lymph node metastasis, emphasizing the usefulness of FDG PET/CT and  
181 lymphoscintigraphy to confirm the diagnosis (14).

182 However, all the above cases proposed that patients who underwent previous  
183 surgery or radiation therapy should receive curative treatments. In our case, the patient  
184 was suspected to have second primary left breast cancer with synchronous CAM by  
185 breast MRI (6,15). We diagnosed second primary left breast cancer by needle biopsy  
186 and synchronous CAM by <sup>99m</sup>Tc and surgical pathology. We believed that CAM was  
187 local lymph node metastasis of the second primary left breast cancer as a result of  
188 changes in lymph node drainage. None of the evidence showed any disease of the right  
189 breast.

190 Because the possibility of contralateral occult breast cancer is very small, mastectomy  
191 is not recommended. We performed left mastectomy and right axillary lymph node  
192 dissection with curative intent.

193

#### 194 **#Conclusions**

195

196 We propose that CAM may occur in second primary or recurrent breast cancer because  
197 of previous surgery or radiation therapy. If changes in lymphatic drainage are suspected  
198 in patients with a history of breast cancer surgery, contralateral axillary lymph node  
199 metastasis should be considered. In patients with recurrent breast cancer, systemic  
200 examinations should be completed for the assessment of lymph node conditions,  
201 especially for the contralateral axillary lymph nodes. CAM could be detected through  
202 preoperative lymphoscintigraphy, lymph node biopsy, and pathological diagnosis. IHC  
203 markers have been shown to usefully distinguish metastatic axillary lymph nodes from

204 occult contralateral tumors. We suggest that isolated CAM without distant organ  
205 involvement represents regional diffusion rather than distant metastasis and recommend  
206 specifying CAM as N3 instead of M1. We should treat CAM with curative intent rather  
207 than palliative intent, and axillary dissection offers good local control.

208

#### 209 **Acknowledgments**

210

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212

#### 213 **Footnote**

214 Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form.

215 The authors have no conflicts of interest to declare.

216 Reporting Checklist: The authors have completed the CARE reporting checklist.

217

218 Availability of data and material: The datasets used and analyzed during the current  
219 study are available from the corresponding author on reasonable request.

220

221 Ethical Statement: The authors are accountable for all aspects of the work in ensuring  
222 that questions related to the accuracy or integrity of any part of the work are  
223 appropriately investigated and resolved. All procedures were in accordance with the  
224 ethical standards of the responsible committee on human experimentation (institutional  
225 and national) and with the Helsinki Declaration. This study was approved by the ethics  
226 and research committee of the First Affiliated Hospital of Nanjing Medical University.  
227 Informed consent was taken from all the patients

228

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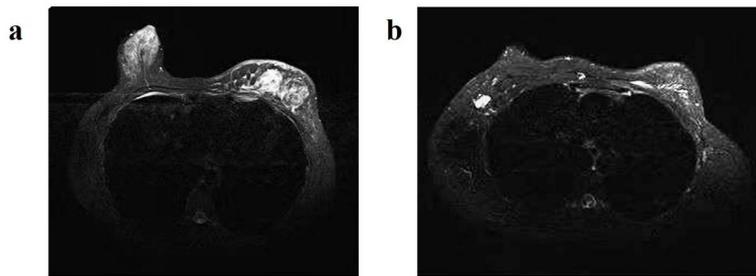
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269 (English Language Editor: C. Betlazar-Maseh)

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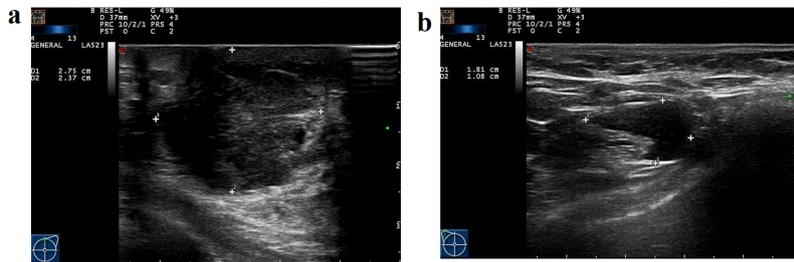
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273

274 **Figure 1** MRI images of the patient's breasts and axillary lymph nodes. **(A)** MRI of the  
275 breast revealed left breast cancer with multiple intra-breast metastases involving the  
276 nipple, areola, and skin, as well as subcutaneous cancerous lymphangitis, and numerous  
277 internal mammary lymph node metastases; **(B)** MRI of axillary lymph nodes revealed  
278 metastasis. MRI: Magnetic resonance imaging.

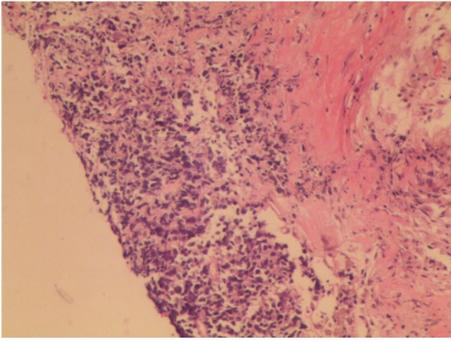
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280

281 **Figure 2** Ultrasound images of the patient's breast and axillary lymph nodes. **(A)** A 2.8  
282 cm × 2.7 cm irregularly shaped and mixed echo mass in the upper quadrant of the left  
283 breast was displayed on ultrasound; **(B)** 1.8 cm × 1.0 cm enlarged lymph node in the  
284 right axilla was displayed on ultrasound.

285



286  
287 **Figure 3** Pathological examination result (HE staining 200×). The left breast mass was  
288 diagnosed as invasive carcinoma by coarse needle puncture. HE: Hematoxylin-Eosin.  
289

批注 [Office1]: Cell map must describe magnification in the Figure Legend (or there is "Scale bar" on the image). Please revise.

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Your Name: Rui Chen

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7	Support for attending meetings and/or travel	None	
8	Patents planned, issued or pending	None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	None	
11	Stock or stock options	None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	None	
13	Other financial or non-financial interests	None	

**Please summarize the above conflict of interest in the following box:**

There is no any conflict of interest.

**Please place an "X" next to the following statement to indicate your agreement:**

  X   I certify that I have answered every question and have not altered the wording of any of the questions on this

**form.**

## ICMJE DISCLOSURE FORM

Date:2021-3-4

Your Name:Qian-Nan Zhu

Manuscript Title:Contralateral axillary lymph node metastasis and molecular changes in second primary breast cancer: a case report

Manuscript number (if known):\_\_\_\_\_ GS-21-137\_\_\_\_\_

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
<b>Time frame: Since the initial planning of the work</b>			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) <b>No time limit for this item.</b>	None	
<b>Time frame: past 36 months</b>			
2	Grants or contracts from any entity (if not indicated in item #1 above).	None	
3	Royalties or licenses	None	
4	Consulting fees	None	

5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	None	
6	Payment for expert testimony	None	
7	Support for attending meetings and/or travel	None	
8	Patents planned, issued or pending	None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	None	
11	Stock or stock options	None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	None	
13	Other financial or non-financial interests	None	

**Please summarize the above conflict of interest in the following box:**

There is no any conflict of interest.

**Please place an "X" next to the following statement to indicate your agreement:**

  X   I certify that I have answered every question and have not altered the wording of any of the questions on this

**form.**

## ICMJE DISCLOSURE FORM

Date: 2021-3-4

Your Name: Xiao-Ming Zha

Manuscript Title: Contralateral axillary lymph node metastasis and molecular changes in second primary breast cancer: a case report

Manuscript number (if known): GS-21-137

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
<b>Time frame: Since the initial planning of the work</b>			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) <b>No time limit for this item.</b>	None	
<b>Time frame: past 36 months</b>			
2	Grants or contracts from any entity (if not indicated in item #1 above).	None	
3	Royalties or licenses	None	
4	Consulting fees	None	

5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	None	
6	Payment for expert testimony	None	
7	Support for attending meetings and/or travel	None	
8	Patents planned, issued or pending	None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	None	
11	Stock or stock options	None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	None	
13	Other financial or non-financial interests	None	

**Please summarize the above conflict of interest in the following box:**

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**Please place an "X" next to the following statement to indicate your agreement:**

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