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Sentinel lymph node localization with contrast-enhanced ultrasound and an I-125 seed: An ideal prospective development study

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HIGHLIGHTS

- The current SLN procedure with nanocolloid is very accurate, though logistically complicated and time consuming.
- A new SLN procedure with microbubbles and an I-125 seed can be performed days or weeks before the surgical SLN procedure.
- SLN localization with microbubbles and an I-125 seed proved not to be a viable alternative to the standard SLN procedure.
- Modifications to this technique did not improve its performance.

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ABSTRACT

Introduction: Our aim was to evaluate the development of microbubble-enhanced sentinel lymph node (SLN) localization with placement of an I-125 seed in breast cancer patients as a potential alternative for SLN localization with nanocolloid. The study is conducted and reported following the IDEAL recommendations for evaluation of a new technique at Stage 2a (Prospective Development Study).
Methods: Fourteen consecutive patients with 15 lesions underwent microbubble-enhanced SLN localization with placement of an I-125 seed after the standard SLN localization (nanocolloid). We placed an I-125 seed within or near the SLN following its identification using intradermally injected microbubbles. The SLN was excised guided by nanocolloid and the SLN containing the I-125 seed was searched for. All technical modifications are described and standardized outcomes measured.
Results: Twelve (80%) microbubble procedures with I-125 seed placements were technically successful. In three cases no microbubble-enhancing lymph node could be detected. Intraoperatively, we found nine I-125 seeds within 0.5 cm of the nanocolloid confirmed SLN. One I-125 seed was found next to a non-SLN and two I-125 seeds were not near any lymph node. Overall, the procedure was successful in 60% (9 out of 15) of the cases.
Conclusion: Given the low success rate, we conclude that microbubble-enhanced SLN is not a viable alternative to the standard SLN procedure. Modifications to this technique did not improve its performance. Planned study (NTR3690 http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3690) was stopped early due to this conclusion and results reported in order to provide a full and transparent record of the evolution of technique.

1. Introduction

Sentinel lymph node biopsy (SLNB) is the standard of care for staging of the axilla. The SLN is conceptually representative of the

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status of the axilla since lymphatic vessels drain to the first "sentinel" node. Several studies have compared overall and disease free survival between patients undergoing SLNB or ALND, and no significant differences were found [1,2], while SLNB was associated with reduced morbidity [3,4]. Histopathological examination of the SLN provides important information on the extent of the disease, the need for ALND [5], as well as prognostic information [6]. The current standard is surgical excision of the sentinel node after preoperative localization with technetium-labelled nanocolloid (technetium-99m), blue dye, or a combination of both. With a combination of both techniques, the sentinel node is successfully localized in over 95% of patients, while the number of false negatives, defined as a sentinel node without malignant cells while other axillary lymph nodes do contain malignant cells, is very low [7–10]. Although this technique is very accurate, the classic SLNB procedure is logistically complicated and time and resource consuming: the technetium takes 1–2 h to reach the sentinel node and because of the half-time of technetium (i.e. 6 h) the excision needs to take place preferably within 24 h. A new, alternative approach to the classic SLNB is microbubble enhanced identification of the SLN followed by radioactive seed localization. Contrast-enhanced ultrasound, by means of intradermal injection of microbubbles, can be used to visualize the lymphatic channels and to identify the SLN [11–16]. After visualization of the sentinel node, an iodine-125 (I-125) seed can be placed percutaneously in or close to the sentinel node. I-125 seeds are increasingly being used for the localization of non-palpable breast tumors [17–19]. An important advantage of the I-125 seed is that it has a longer half-life than technetium (i.e. 59.4 days versus 6 h). It can therefore be placed days or weeks before surgery and detaches the preoperative procedures from the surgery itself, making planning less complicated.

New minimally invasive procedures, as the microbubble-enhanced SLN localization, are complex procedures that are challenged by factors that depend on operator, team, and setting. A 5-stage framework was introduced for scientific evaluation of these innovations: the IDEAL recommendations [20]. These recommendations describe 5 stages of development that occur when new interventional procedures are evaluated and introduced into clinical practice: Idea, Development, Exploration, Assessment, and Long-term study (http://www.ideal-collaboration.net).

In this study, we report a prospective development study (IDEAL stage 2a) of microbubble enhanced SLN localization with placement of an I-125 seed in patients with breast cancer, in terms of technical modifications and development, feasibility, safety and, technical success rate.

2. Materials & methods

2.1. Patient population

We report the first 14 consecutive patients undergoing microbubble enhanced SLN localization with placement of an I-125 seed for 15 breast cancers. Patients were recruited between November 2012 and April 2014. The study was approved by the ethical committee of the University Medical Center Utrecht, The Netherlands, and written informed consent was obtained from all participants. We registered this single center study on the Dutch Trial Register (NTR3690 http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3690). All female breast cancer patients of 18 years and older with indication for SLNB were eligible. Exclusion criteria were proven tumor-positive lymph nodes, SLNB after neoadjuvant chemotherapy, and patients with severe cardiac, lung or neurologic disease.

2.2. SLN localization

One day before surgery, we performed the standard SLN localization with technetium nanocolloid (Nanocoll, GE Healthcare, Saluggia, Italy). A mean dosage of 370 MBq Technetium in a volume of 0.3 mL was injected periareolarly in two depots. After 1.5–2 h, lymphoscintygraphy of the involved breast and axilla was performed in both lateral and anterior projections. Lymph nodes identified in this way were taken as the true sentinel node and formed the gold standard.

Two dedicated breast radiologists (RP, AF) performed the microbubble-enhanced SLN localization [14]. On the day of surgery, the microbubbles (SonoVue, Bracco Imaging, Milan, Italy) were injected as reported in detail by Sever et al. [15]. In short, between 0.2 and 0.4 mL of microbubble suspension was injected into and just under the skin of the areola in the upper outer quadrant of the affected breast using a 1 mL syringe and 25-gauge needle. After injection of the microbubble suspension, we visualized the lymphatic channels on ultrasound (Philips iU22 scanner, Philips Medical Systems, Best, The Netherlands) with contrast pulse sequencing and followed the lymphatics towards the axilla. The contrast accumulated in the axillary lymph nodes and grey-scale ultrasound confirmed presence of a lymph node. Under grey-scale ultrasound guidance, we placed an I-125 seed (single packed pre-loaded needles; Best Medical International, Springfield, Virginia, USA) within or near this lymph node. When we could not identify any obvious lymph node, the procedure was repeated up to four consecutive injections of microbubbles. If by then no lymph node had been identified, the study was abandoned and accepted as a technical failure.

After radiological localization of the sentinel node, we performed SPECT/CT imaging (Siemens Symbia 16T, Siemens, Erlangen, Germany) of the axilla. A nuclear medicine physician assessed the concordance of the Technetium sentinel node and microbubble sentinel node.

2.3. Surgical procedure

We performed the surgical excision of the sentinel node in standard fashion: technetium nanocolloid guided and optionally accompanied by injection of blue dye, according to the surgeons discretion. After a skin incision, the technetium 'hot' SLN was actively searched for, using the gamma probe (Europrobe, Strassbourg, France) on 140-keV and the node was excised. Subsequently, we switched the gamma probe to 27-keV to detect I-125 and searched the specimen for presence of the I-125 seed. If the seed was present in/near the excised lymph node, we confirmed absence of radioactivity in the axilla with the gamma probe and the SLNB procedure was completed. If the I-125 seed was not present in the excised specimen, it was searched for in the axilla and excised, including possible lymph node(s) surrounding the I-125 seed (within a range of 0.5 cm). We marked this specimen in a different way than the technetium lymph node. After completion of the SLNB, the primary breast tumor was excised.

2.4. Pathology

With help of a contamination monitor, we measured the excised axillary specimen and extracted the I-125 seed by making a small incision. Subsequently, we counted the total number of lymph nodes and a dedicated breast pathologist determined tumor positivity. The technetium and I-125 labelled lymph nodes were specially mentioned in the report.

2.5. Outcomes

IDEAL recommendations for this Prospective Development Study (PDS) stage of development are to measure standardized outcomes, assessing safety, technical feasibility, and success rate. For safety, we assessed procedure-related complications, defined as severe hematomas due to the injection of microbubbles or I-125 seed, I-125 seed migration, and allergic reactions. We defined technical feasibility as a successful microbubble procedure with visualization of the sentinel node followed by successful placement of an I-125 seed. The success rate was defined as correct localization of the sentinel node with placement of the I-125 seed within 0.5 cm of the node, assessed intraoperatively. Demographics, radiological, clinical and histologic characteristics were described as proportions and means with standard deviation.

Table 1
Baseline characteristics of all patients undergoing microbubble-enhanced SLN localization.

Patients	$N = 14$	%
Median age in years (range)	56.0 (41–68)	
Reason for referral		
Screening	6	43
General practitioner	5	36
Radiology department	3	21
Family history		
Positive	8	57
Negative	6	43
Menopausal status		
Premenopausal	4	29
Perimenopausal	2	14
Postmenopausal	8	57
Lesions	**$N = 15$**	**%**
Palpability		
Palpable	11	73
Non-palpable	4	27
Location of lesion		
Upper outer quadrant	10	67
Lower outer quadrant	3	20
Central	1	7
Upper inner quadrant	1	7
Axillary lymph nodes		
Non-palpable	12	80
Palpable	3	20
Presentation on mammogram		
Mass	8	53
Mass with microcalcifications	2	13
Microcalcifications only	2	13
Not visible on mammogram	3	20
Lesion visibility on ultrasound		
Visible	13	87
Not visible	2	13
Median lesion diameter on ultrasound (range)	1.6 (0.7–4.0)	
BIRADS classification		
IV	5	33
V	10	67
Biopsy		
Ultrasound-guided	13	87
Stereotactic guidance	2	13
Cytology of axillary lymph node taken		
No	12	80
Yes	3	20
Diagnosis breast		
Invasive ductal carcinoma	10	67
Invasive lobular carcinoma	2	13
Invasive ductolobular carcinoma	2	13
Ductal carcinoma *in situ*	1	7

3. Results

The median age of the 14 patients was 56.0 years ranging from 41 to 68 years (Table 1). A total of 15 lesions were found in these patients and 11/15 lesions (73%) were palpable. On mammography, 10/15 lesions presented as a mass lesion with or without microcalcifications, two lesions presented as microcalcifications only, and three lesions were not visible on mammography due to very dense breast tissue. Ten lesions were classified as BIRADS 5 and five as BIRADS 4. Preoperative axillary ultrasound showed suspicious lymph nodes in three patients. Fine needle aspiration of these nodes showed no malignant cells. Histopathological examination of the breast lesions showed 10/15 invasive ductal carcinomas, 2 invasive lobular carcinomas, 2 invasive ductolobular carcinomas and 1 ductal carcinoma *in situ* grade 3.

3.1. Microbubble enhanced localization of the SLN

The microbubble procedure was performed for localization of 15 sentinel nodes. In all patients, immediately following injection, the lymphatic channels enhanced and in six patients an enhancing axillary lymph node was observed. In three of these nodes, an I-125 seed was placed. A second injection was given to 12 patients and the lymph node of 8 patients enhanced. An I-125 seed was placed in 6 of these enhancing lymph nodes (Fig. 1, Fig. 2). A third injection was performed in 6 patients, of whom 3 lymph nodes enhanced and an I-125 seed was placed. A fourth attempt was made in 1 patient, however, no lymph node could be found. In total, 12 (80%) microbubble procedures resulting I-125 seed placements were performed, while in three cases (20%) the procedure failed to visualize the SLN.

3.2. Surgical and pathological analysis

The technetium labeled sentinel node was retrieved in all 12 patients with a successfully placed I-125 seed. After the technetium-guided SLNB, additional tissue was removed in two patients, to retrieve the I-125 seed. In 9 patients, the I-125 seed was found within 0.5 cm of the technetium-identified SLN. Of these, four were found within the sentinel node and the other five near the sentinel node. One I-125 seed was found in the close vicinity of a non-sentinel node and two were not near any lymph node (Table 2).

Final histology showed a macrometastasis in one patient, a micrometastasis in one and isolated tumor cells in one patient.

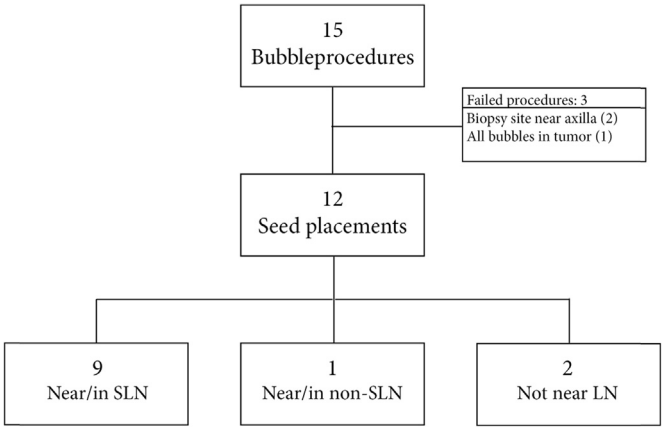

Fig. 1. Flowchart of the study results.

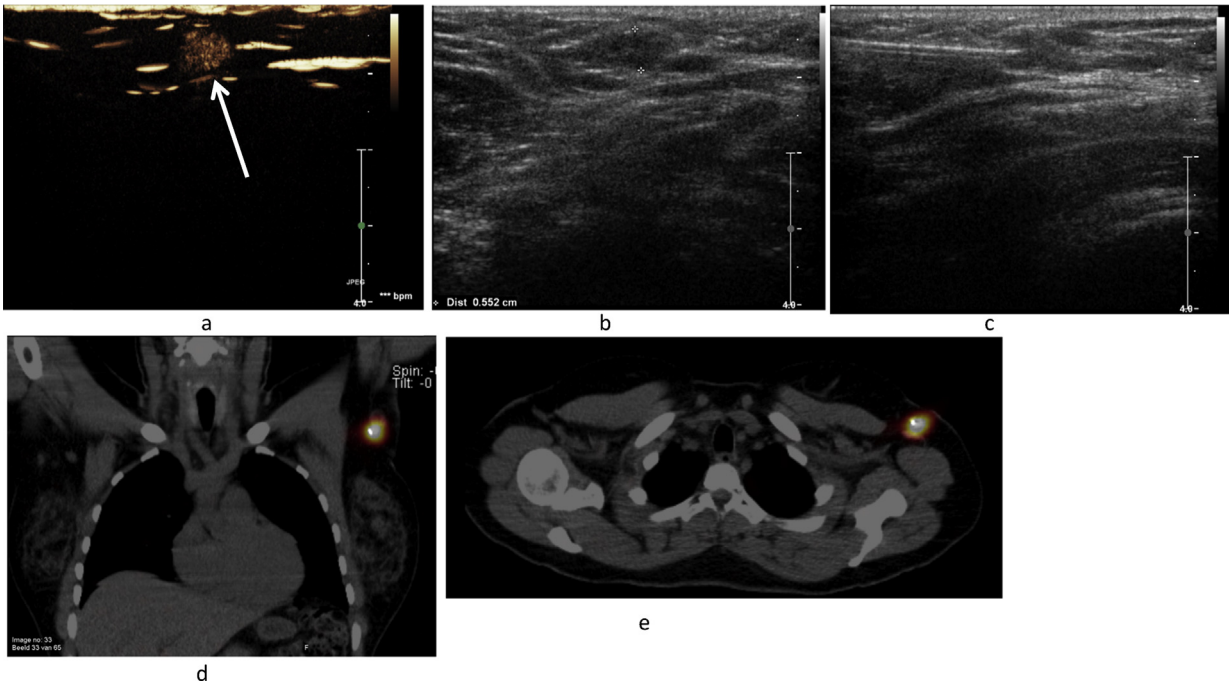

Fig. 2. 41-year old woman with invasive ductal carcinoma – a) microbubble procedure, showing an enhancing lymph node (white arrow), b) corresponding grey-scale image, c) grey-scale image sowing the radioactive seed placement, d) and e) SPECT-CT imaging after placement of the seed with the seed (bright) and the technetium-enhancement (yellow/orange).

Table 2
Overview of the radiological outcomes of the microbubble procedures with I-125 seed placement.

Case no.	Enhancing lymph node 1st attempt	I-125 seed placed	Enhancing lymph node 2nd attempt	I-125 seed placed	Enhancing lymph node 3rd attempt	I-125 seed placed	Enhancing lymph node 4th attempt	I-125 seed placed	Concordance Tc-99m & I-125 lymph node	In/near LN
1	No	No	No	No	Yes	Yes			Same node	in
2	No	No	Yes	Yes					Same node	in
3	Yes	Yes							Same node	near
4	No	No	Yes	No	Yes	Yes			Same node	near
5	No	No	No	No	No	No			n/a	n/a
6	Yes	No	Yes	Yes					Same node	near
7	Yes	No	Yes	Yes					Same node	near
8	Yes	Yes							Other node	near
9	No	No	No	No	No	No			n/a	n/a
10	No	No	Yes	Yes					Same node	in
11	No	No	Yes	Yes					Same node	in
12	Yes	Yes							No LN near I-125	>0.5 cm
13	No	No	Yes	No	Yes	Yes			No LN near I-125	>0.5 cm
14	Yes	No	Yes	Yes					Same node	near
15	No	No	No	No	No	No	No	No	n/a	n/a

Abbreviations: LN: lymph node; I-125 seed: Iodine-125 seed; Tc-99m: Technetium-99m nanocolloid; n/a: not applicable.
Blank cells indicate that a subsequent injection of microbubble contrast was not performed.

3.3. Technical adjustments and technical success

We were unable to visualize the SLN with microbubbles in three patients (consecutive procedure numbers 5, 9, and 15) (Table 2). We adjusted the microbubble procedure in two of these cases (number 9 and 15). In these patients, the microbubbles accumulated in a biopsy site in the upper outer quadrant of the breast (#9) and in the primary breast tumor (#15). We adjusted the procedure by injecting the microbubbles more towards the axilla. This resulted in better visualization of the lymphatic vessels, however, did not results in visualization of a lymph node.

During the study, we aimed to place the I-125 seed within the lymph node. However, due to the fat tissue in the axilla and relatively small lymph nodes, it was found very hard to correctly place the seed within the lymph node. No adjustments could be made to improve the correct seed placement.

Overall, technical success of the new procedure was achieved in 12/15 (80%) microbubble procedures with placement of an I-125 seed next to the node. No procedure-related complications were observed. Success rate of the localization, i.e. surgical retrieval of the SLN with the I-125 seed within 0.5 cm of the node, was obtained in 9/15 (60%) localizations. In 4/15 (27%) patients, the I-125 seed was found within the SLN and in 5/15 (33%) patients near the SLN. From surgical perspective, placement of the seed near the SLN is not accurate enough and might result in a node picking procedure. For this reason, the study was stopped at 14 patients due to the conclusion that this technique was not able to replace the current standard SLNB procedure.

4. Discussion

The current standard for staging of the axilla is surgical excision of the SLN. In this prospective development study we evaluated the first results of a new axillary staging technique according to the IDEAL recommendations for this stage. With microbubble enhanced ultrasound, the SLN can be localized preoperatively at the radiology department and an I-125 seed can be placed days or weeks in advance of the surgery. We showed that we were able to visualize 12/15 axillary lymph nodes with microbubbles and placed an I-125 seed in all 12. In 9/12 patients, the same lymph node was identified by microbubbles as with technetium nanocolloid.

We evaluated the efficacy of this new technique according to the IDEAL-guidelines (stage 2a) in a small group of patients. Evaluation of new techniques by systematic criteria enables researchers to make validated decisions regarding the development of a technique. It enables researchers to decide whether or not to pursue a novel technique. Furthermore, it helps other researchers by providing information on encountered problems, modifications to the technique and could save others from trying ineffective procedures. In line with the IDEAL criteria, we modified the technique in subsequent patients. Injection of the microbubbles more craniolateral towards the axilla did not result in visualization of a lymph node. We were unable to adjust the technique further to obtain a higher success rate.

There would most likely be presence of a learning curve in the microbubble-enhanced localization of the sentinel node, contributing to our results with the inclusion of only 15 patients. However, the two dedicated breast radiologists who performed the procedures had over 20 year experience in the localization of breast and axillary lesions and were specifically trained by Ali Sever to perform the microbubble procedure. The localization of the sentinel node was considered adequate with visualization of the node in 12/15 patients. The main drawback of the technique, however, was to correctly place the I-125 seed inside relatively small lymph nodes.

Sever and colleagues pioneered the microbubble localization of SLNs in breast cancer patients [21]. In their most recent study, they were able to visualize the sentinel node in 333/347 (96%) patients. This percentage is higher than achieved in earlier work, with detection rates ranging from 89% to 93% [12,13,16], which also suggests the presence of a learning curve. The group of Sever is the only group that published their results on microbubble-enhanced localization of the sentinel node. They found high rates of visualization of the sentinel node, but generalizability is limited due to the single center experience.

After preoperative visualization of the microbubbles, Sever et al. biopsied the lymph nodes in order to avoid a two-step axillary surgery. Some 35 patients had a positive preoperative lymph node biopsy and directly underwent a complete axillary lymph node dissection (ALND). In these 35 patients, 29 had a macrometastasis and the other 6 had isolated tumor cells or micrometastasis and an ALND may have been overtreatment of the axilla in the latter 6 patients [16]. Undersampling was also present with 22 false-negative results, resulting in a sensitivity of 61%. They conclude that identification and biopsy of the sentinel node using microbubbles in its current form should not replace the surgical SLNB. This is underlined by the results from pooled analysis from these three studies, showing that this technique was inferior to the standard dual tracer technique [22]. Modifications to the technique may lead to a change in the SLN procedure. Diepstraten et al. preoperatively removed the microbubble-enhanced SLN in five patients [23]. In three women the sentinel node was removed with a radiofrequency-assisted breast lesion excision system and in two women by means of vacuum-assisted large core needle biopsy. Further research is necessary and larger samples sizes need to be evaluated.

Several other new and promising techniques have been introduced to localize the sentinel node in breast cancer patients. Indocyanine Green (ICG) is one of these promising techniques. The ICG is injected intradermally and transported through the lymphatic vessels into the axillary lymph node. With near-infrared fluorescence the ICG can be visualized intraopertatively [24]. ICG is often combined with a radioactive tracer and in a recent systematic review, SLN identification ranged between 93.1% and 100% [22]. Pooled data analysis showed no significant difference between ICG and nanocolloid in SLN identification. The only randomized controlled trial for ICG in breast cancer patients compared the use of a combination of nanocolloid, ICG and blue dye with the combination of nanocolloid and ICG only [25]. They found no benefit for the use of blue dye additionally to ICG and nanocolloid. They were able to localize the sentinel node with ICG only and succeeded in 75% of patients [25].

Another promising technique for SLN localization is by using supraparamagnetic iron oxide (SPIO). Here, the SPIO is injected subcutaneously in the operating room. During surgery, the surgeon used a handheld magnetometer for skin localization of the SLN and the gamma probe was used to confirm the location [26]. The identification rate of the sentinel node with the standard technique was 95% (152/160 patients) versus 64% (151/160) patients with the magnetic technique. Two patients in whom the magnetic technique was not successful had a macrometastasis. The magnetic technique was found to be non-inferior to the standard approach [26].

5. Conclusion

This is the first study to evaluate microbubble-enhanced SLN localization with placement of an I-125 seed. We were able to place an I-125 seed in the vast majority of patients, however, exact placement of the I-125 seed inside the sentinel node remains challenging in a clinically negative axilla. We were unable to increase the success rate of this procedure and would therefore not advice continuation of the evaluation of this technique to a prospective exploration stage.

Ethical approval

The study (METC 11-543) was approved by the ethical committee of the University Medical Center Utrecht, The Netherlands, and written informed consent was obtained from all participants.

We registered this single center study on the Dutch Trial Register (NTR3690 http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3690).

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Author contribution

Study concepts: MB, HV, AS, RP, MH, AW, MvdB.
Study design: MB, HV, RP, MvdB.
Data acquisition: MB, RP, MF, PvD, CvdP, AW, MH.
Statistical analysis: MB, HV.
Manuscript preparation: MB.
Manuscript editing: all authors.
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Conflicts of interest

None to declare.

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