

# Sentinel Node Biopsy Versus Low Axillary Sampling in Predicting Nodal Status of Postchemotherapy Axilla in Women With Breast Cancer

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## abstract

**PURPOSE** We tested low axillary sampling (LAS) and sentinel node biopsy (SNB) performed in the same patient to predict axillary nodal status post-neoadjuvant chemotherapy (NACT) in women undergoing elective breast surgery, clinically NO after NACT.

**PATIENTS AND METHODS** A total of 751 women clinically node negative post-NACT underwent LAS (excision of lymph node [LN] and fat below first intercostobrachial nerve). Of these women, 730 also underwent SNB by dual technique (methylene blue plus radioisotope). SNB (defined as targeted plus palpable LNs) and LAS specimens were distinctly examined for metastasis. All patients underwent completion axillary lymph node dissection. Post-NACT, 290 (38.6%) of 751 women had residual positive lymph nodes on pathology.

**RESULTS** The median clinical tumor size was 5 cm (range, 1-15 cm), and 533 (71%) of patients were N1 or N2 at presentation. Targeted sentinel node (SN) identification was 85.7% (626 of 730; median, two LNs); SN with palpable nodes was found in 95.2% (695 of 730; median, five LNs); LAS node was identified in 98.5% (740 of 751; median, seven LNs). In all but one case, the SN was found within the LAS specimen. The false negative rate (FNR) of SNB (blue, hot, and adjacent palpable nodes) was 19.7% (47 of 238; one-sided 95% CI upper limit, 24.0), compared with an FNR of 9.9% for LAS (29 of 292; one-sided 95% CI upper limit, 12.8;  $P < .001$ ). If SNB was confined to blue/hot node, excluding adjacent palpable nodes, the FNR was 31.6% (74 of 234; one-sided 95% CI upper limit, 36.6). The FNR could be brought down to  $< 8.8\%$  if three or more LNs were identified by LAS.

**CONCLUSION** LAS is superior to SNB in identification rate, FNR, and negative predictive value in predicting node-negative axilla post-NACT. LAS can be safely used to predict negative axilla with  $< 10\%$  chance of leaving residual disease.

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## INTRODUCTION

Axillary lymph node (LN) dissection (ALND) in breast cancer is therapeutic primarily in node positive and advanced cancers, but it results in lymphoedema, lymphangitis, restricted shoulder mobility, and loss of sensation in the inner aspect of the arm. Furthermore, the arm then needs to be protected lifelong from injury and insult. Currently, in node-negative early breast cancer, limited axillary surgery with sentinel node (SN) biopsy (SNB) alone is the standard of care and is associated with low regional failure rates.<sup>1-9</sup> In some centers, four-node axillary nodal sampling<sup>10</sup> or low axillary sampling (LAS)<sup>11</sup> has been shown to have an equivalent false negative rate (FNR) and is routinely offered to aid in deciding on the need for ALND. In low-

to middle-income countries, LAS also avoids use of radiocolloid and can be adapted where a lack of nuclear medicine centers limits the use of gamma probes.

The evidence for limited axillary surgery is not so robust in women who become node negative after receiving neoadjuvant chemotherapy (NACT) for large and locally advanced breast cancer. In this subset of patients with higher-risk cancers and higher nodal disease,<sup>12</sup> we await evidence on the safety of limited axillary nodal surgery. It is also well known that the LN yield after NACT is lower, and false negativity may be increased by virtue of a lower nodal pickup.<sup>13-16</sup>

Current evidence in the literature is varied regarding postchemotherapy node-negative status, with some

## ASSOCIATED CONTENT

### Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

We compared the novel technique of low axillary sampling (LAS) with sentinel node biopsy (SNB) to predict axillary nodal status post–neoadjuvant chemotherapy (NACT) in women undergoing elective breast surgery, clinically NO after NACT.

### Knowledge Generated

SNB had a false negative rate (FNR) of 19.7% (95% confidence interval [CI] one-sided upper limit, 24) in axilla clinically NO after NACT. LAS of lower axillary nodes and fat defined by anatomic boundaries improved the FNR to 9.9%, with a one-sided 95% CI upper limit of 12.8 ( $P < .001$ ) and negative predictive value of 94.0%. Also, identifying three or more lymph nodes (LNs) lowered the LAS FNR to 8.8%; therefore, removal of three or more LNs is recommended for best results.

### Relevance

LAS is clearly superior to SNB in identification rate, FNR, and NPV post-NACT, with  $< 10\%$  chance of leaving residual disease, independent of disease biology. It can be considered a suitable alternative in countries with limited resources, where disease is detected at a more advanced stage, larger tumors and higher grade, and nuclear medicine facilities or gamma probe procedures are not available.

studies remaining noncommittal or reasoning against the reliability of the procedure<sup>13-15</sup> and others supporting the role of SNB after chemotherapy.<sup>17-23</sup> Xing et al<sup>24</sup> reported a large meta-analysis in 2006 from MD Anderson Cancer Center that included 1,273 patients from 21 level IIb exploratory cohort studies. The pooled estimate identification rate was 90%, sensitivity was 88%, and the FNR was 12% overall (with the largest FNR at 33% in one study).

The issue of the timing of the procedure also remains controversial (ie, SNB before or after chemotherapy).<sup>25-27</sup> The recommendations are different for cNO and cN+ nodes. When upfront SNB is practiced, a patient with previously cNO disease for whom chemotherapy is planned could be subjected to limited axillary surgery post-chemotherapy with a low FNR. However, in the case of a positive SN upfront, there are two major concerns after chemotherapy. The FNR is  $> 10\%$  in such patients post-NACT, and if considered for complete axillary clearance in view of a previous positive node, patients may end up being denied the possibility of axillary conservation even after complete axillary response to systemic therapy, as seen in triple-negative breast cancer (TNBC) or human epidermal growth factor receptor 2 (HER2)–positive tumors after targeted therapy.

In a clinically node-positive axilla prechemotherapy, identification of the positive node with a radioopaque marker is known to reduce the FNR after chemotherapy.<sup>28-30</sup> Post-chemotherapy, axillary sonography<sup>31</sup> with fine-needle aspiration cytology (FNAC), along with marking any suspicious node with a clip or suitable radioactive marker<sup>28</sup> and ensuring removal of such nodes at surgery, reduces the FNR.

Guidelines currently recommend SNB as a 2B recommendation after NACT because of the high FNR. The ACOSOG Z1071 trial<sup>30-32</sup> including 756 women reported an FNR of 12.6% with identification of two SNs and 31.5% with

identification of one SN. In the SENTINA (ClinicalTrials.gov identifier: [NCT02031042](https://clinicaltrials.gov/ct2/show/study/NCT02031042)) study,<sup>33</sup> only arm C was relevant; in 592 patients, the FNR was 9.6% when two or more SNs were found.

Here we report the results of a prospective comparative study of targeted SNB versus LAS for the prediction of the status of remaining axillary nodes with an acceptable FNR in post-NACT axilla.

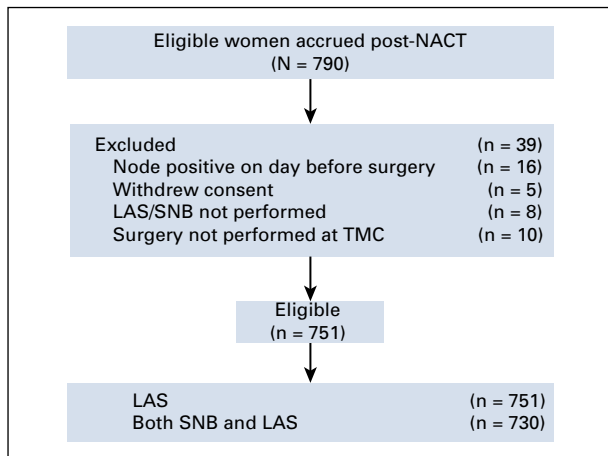
## PATIENTS AND METHODS

### Study Methodology

The study involved anatomically guided LAS of all fat and LNs below the first intercostobrachial nerve in eligible patients providing informed consent. SNB identification was by dual technique using technetium-labeled sulfur colloid and methylene blue dye in the same patient. SNB and LAS were validated by completion axillary clearance in all patients. All nodes were appropriately dissected, labeled, and analyzed as described.

### Sample Size Calculation

In our initial study<sup>34</sup> in 209 women reported at the ASCO 2012 Annual Meeting, the FNRs for SNB and LAS post-NACT were 14.4% and 8.5%, respectively, suggesting superiority of LAS over SNB. However, although the overlapping and wide confidence interval (CI) indicated that the two procedures were comparable, the sample size was small and needed to be repowered to prove equivalence. On the basis of the reference FNR of 9.8% from the NSABP B32 study,<sup>3</sup> an FNR of 10% is considered acceptable in early breast cancer. Adhering to the same standard, our sample size was recalculated for LAS and SNB in the post-NACT setting. We would require a minimum of 750 patients for a 10% FNR with a 95% CI upper limit of 12 for adequate power to prove the acceptability of LAS in this subset of patients. An additional 40 patients



**FIG 1.** Study flow diagram. LAS, low axillary sampling; SNB, sentinel node biopsy; TMC, Tata Memorial Centre.

were added later as an amendment to compensate for patients not accrued as a result of an axillary node becoming palpable on the day of surgery or withdrawal of consent.

**Patients**

Ours was a single-institution study carried out from 2012 to 2018 by three consultant surgeons in a single breast unit following standard predefined protocols. The standard unit protocol is to administer NACT to women with clinically large operable breast cancer or locally advanced breast cancer (T3-4, N any, MO). Prechemotherapy axilla was not subjected to sonoguided biopsy confirmation of nodal metastasis before the start of chemotherapy, because this was not a part of standard unit protocol during that time period. Patients with early breast cancer receiving NACT for breast/tumor ratio to enable breast conservation were excluded from the study. Women who became clinically node negative post-NACT were recruited to the study after providing informed consent (institutional review board approved).

A subdermal injection of 0.5 mL of technetium-99–labeled filtered sulfur colloid (1 mCi) was administered 2 hours before surgery. A preoperative scintiscan confirming uptake in the tumor and SN was performed only in first few patients. Ten minutes before commencement of axillary dissection, 0.5 mL of blue dye (1% methylene blue) was injected intradermally into the area overlying the tumor. Gentle breast massage was carried out, and presence of a hotspot was confirmed in the axilla with a handheld gamma probe. All patients first underwent the LAS procedure, carried out through a 3- to 4-cm axillary incision. The anatomic boundaries of LAS were defined anteriorly by the under surface of the pectoralis major, posteriorly by the latissimus dorsi, medially by the second digitation of the serratus anterior, superiorly by the intercostobrachial nerve, and inferiorly to include the axillary tail.<sup>11</sup>

For the LAS specimen (fat and LNs) removed, an ex vivo count was performed, noting blue and/or hot nodes with any immediately adjacent enlarged palpable nodes, as well as an in vivo count, checking for SNs outside the LAS specimen in the axilla. All this information was meticulously documented as SNs were dissected (defined as blue and/or hot nodes with any palpable adjacent nodes) and sent for frozen section evaluation to confirm and separately label all nodes. This was followed by complete axillary dissection up to level III LNs in all patients.

Radioactive nodes (ie, hot nodes) were defined as LNs with a count rate of  $\geq 10$  times the background count, with 10% of the count at the primary injection site in the breast. All blue-stained LNs and any additional non-blue-stained LNs with an afferent blue lymphatic channel were labeled blue nodes. All were included as SNs. The rest of the axillary tissue was also examined for blue and/or hot nodes, and if found, these were also included as SNs. All LNs harvested by LAS or SNB were bisected. One half were subjected to hematoxylin and eosin staining in a single-section analysis at frozen section. Both halves were subsequently assessed by definitive histopathology after paraffin embedding. The frozen section and final histopathologic evaluations were performed using a single section per LN.

**TABLE 1.** Patient and Tumor Characteristics (N = 751)

Characteristic	No. of Patients	(%)
Age, years		
≤ 50	537	71.5
> 50	214	28.5
Tumor location		
Outer half	362	48.2
Inner half and central	296	39.4
Multicentric	80	10.7
Unknown	13	1.7
cT size		
T1	15	2.0
T2	378	50.3
T3	358	47.7
Tumor receptor status		
ER positive		44.4
PgR positive		32.2
CerbB2 positive 3+		20.2
cN: pre-NACT clinical node status		
LN impalpable/soft	218	29
LN palpable suspect/hard	533	71
ypN: axillary node metastasis		
Node negative	461	61.4
Node positive	290	38.6

Abbreviations: ER, estrogen receptor; N, node; NACT, neoadjuvant chemotherapy; PgR, progesterone receptor.

**TABLE 2.** Targeted SNB Validation Compared With Remaining Axillary Nodes (n = 636 of 730)

Targeted SNB Validation	Remaining Axillary LNs		Total
	Positive	Negative	
SNB			
Positive	102	58	160
Negative	74	392	466
Total	176	450	626

Abbreviations: LN, lymph node; SNB, sentinal node biopsy.

The rest of the dissected axillary LNs were assessed similarly.<sup>11</sup> Final histopathologic evaluation followed the ASCO–College of American Pathologists guidelines. Immunohistochemistry (IHC) was not used to detect metastatic cells in LNs.

**RESULTS**

A total of 790 eligible women were included in the study. Of these, effectively, 751 eligible women underwent LAS and 730 underwent both LAS and SNB with blue dye and/or radiocolloid injection (Fig 1), followed by completion axillary clearance in all women. The median clinical tumor size before starting chemotherapy was 5 cm (range, 1-15 cm), the median postchemotherapy pathologic tumor size was 2 cm, and residual axillary node positivity was 38.6% (Table 1).

**Targeted SNB**

SNs were identified by targeting in 626 (85.7%) of 730 patients, with a median of two blue or hot nodes with false negative reporting in 74 (31.6%) of 234 patients and a negative predictive value (NPV) of 84.1% (n = 392 of 466; Table 2).

**Targeted SNB With Palpable Adjacent Node**

When SNB also included the adjacent palpable node, the yield was better. In 695 (95.2%) of 730 patients with a median of five LNs in whom the status of the axilla could be predicted, we found an FNR of 19.7% with a one-sided 95% CI upper limit of 24 (n = 47 of 238; Table 3) and an NPV of 90.1% (n = 457 of 504).

**LAS**

LAS was successful in 740 (98.5%) of 751 patients, with a median of seven LNs identified and an FNR of 9.9% (one-sided 95% CI upper limit, 12.8; 29 of 292 patients) and NPV of 94.0% (448 of 477 patients; Table 4). Of those patients in whom no node was found in sampling, two had a total yield of fewer than five LNs in the rest of the axilla; in the remaining patients, total yield was < 10 LNs in the axillary dissection. The probable explanation for this is that the effect of chemotherapy on diseased LNs resulted in the complete disappearance of nodal architecture, with a reduced effective nodal yield. LAS and targeted SNB with or

**TABLE 3.** Targeted SNB Plus Palpable Adjacent Node Biopsy Validation Compared With Remaining Axillary Nodes (n = 695 of 730)

SNB Plus Palpable Node Validation	Remaining Axillary LNs		Total
	Positive	Negative	
SNB plus palpable node biopsy			
Positive	92	99	191
Negative	47	457	504
Total	139	556	695

Abbreviations: LN, lymph node; SNB, sentinal node biopsy.

without palpable LNs were then compared for the impact of the number of LNs dissected and the FNR and NPV. Results are summarized in Tables 5 and 6.

Presence of lymphovascular invasion (LVI) is known to have a poor impact on outcome and is correlated with the presence of nodal metastasis. In our study, LVI was reported in 681 patients, of whom LVI was positive in 153 (22.5%) of patients and absent in 528 (77.5%). As expected, positive LVI compared with negative LVI correlated with higher axillary disease (72.5% v 30.5%) and more positive LAS nodes (66.0% v 28.3%). Interestingly, the FNR for LAS was similar in LVI-positive and -negative patients, at 9% and 8.6%, respectively. The 55 patients with unknown LVI were excluded from this analysis.

**DISCUSSION**

The management of the axilla in early breast cancer is clearly moving away from surgery and toward radiation therapy in the presence of low disease burden in the axillary nodes; however, this is not the case for postchemotherapy status in larger tumors and in patients with a heavy burden of disease in the axilla. Currently, even with reduced nodal disease burden after chemotherapy, the axilla is still being treated with caution, with completion ALND.

In 218 of 751 women, there were clinically impalpable or nonsuspicious axillary nodes before starting chemotherapy (cNx), and the remaining women had palpable suspicious or positive axillary nodes (cN1/cN2). In this study, axillary ultrasound or FNAC was not performed to confirm node-positive status before chemotherapy. More recently, it has

**TABLE 4.** LAS Validation Compared With Remaining Axillary Nodes (n = 740 of 751)

LAS Validation	Remaining Axillary LNs		Total
	Positive	Negative	
LAS			
Positive	128	135	263
Negative	29	448	477
Total	157	583	740

Abbreviations: LAS, low axillary sampling; LN, lymph node.



**TABLE 5.** Comparative Results of SNB (bias and hidden) Alone Versus LAS Versus SNB Palpable

Variable	Percentage		
	Targeted SNB (bias and hidden) Alone (n = 626 of 730)	LAS (n = 740 of 751)	SNB Palpable (n = 695 of 730)
Identification	85.7	98.5	95.2
FNR	31.6	9.9	19.7
NPV	84.1	94.0	90.7
Sensitivity	47.1	81.5	66.2

NOTE.  $P < .001$ .

Abbreviations: FNR, false negative rate; LAS, low axillary sampling; NPV, negative predictive value; SNB, sentinel node biopsy.

been recommended that to further reduce the FNR, any of the following methods may be considered: clipping the node prechemotherapy at the time of ultrasound-guided FNAC, marking the suspicious or positive axillary node with tattooing, or repeating ultrasound after NACT before surgery for axillary nodal status and at the time of SNB and surgery to remove the targeted or clipped node.<sup>28,29,30,35,36</sup> At the time of the start of this study, such imaging and node marking were not standard in our institution because of cost limitations.

The GANEA 2 (ClinicalTrials.gov identifier: [NCT01221688](https://clinicaltrials.gov/ct2/show/study/NCT01221688)) study<sup>37</sup> was a French multi-institutional study that examined outcomes in 957 women with large operable breast cancer who were to receive NACT. Those who were cytologically positive in the axilla underwent post-NACT SNB and lymphadenectomy. Those who were cNO or for whom N1 status could not be confirmed on FNAC prechemotherapy underwent SLN post-NACT, followed by lymphadenectomy when positive or inconclusive. Those with pre-NACT cNO status had a post-NACT SN identification rate of 95%, with an FNR of 9%. Those with pN1 status had a lower post-NACT SN identification rate of 82%, with an FNR of 11.7% (95% CI, 7.3% to 17.9%). Both residual tumor size > 5 mm and LVI were independent predictors for involved ALND.

**TABLE 6.** FNR, Sensitivity, and NPV per Number of LNs Identified

No. of LNs	Percentage		
	FNR	Sensitivity	NPV
LAS			
1-2	22.7	66.6	89.1
≥ 3	8.8	83.0	94.4
SNB plus palpable node biopsy			
1-2	40.0	50.0	87.5
≥ 3	18.3	67.7	91.0

Abbreviations: FNR, false negative rate; LAS, low axillary sampling; LN, lymph node; NPV, negative predictive value; SNB, sentinel node biopsy.

In our study, too, presence of LVI correlated with both higher axillary sampling nodal positivity and residual disease in the rest of the axilla. However, the FNR was not different in LVI-positive versus -negative patients (9% v 8.6%, respectively).

It is known that the FNR decreases if a larger number of SNs are identified. In fact, dissection of three or more SNs easily helps keep the FNR < 10%.<sup>38</sup> In the ACOSOG Z1071<sup>36</sup> and SENTINA trials,<sup>33</sup> only 56% and 34% of patients, respectively, had three or more SNs removed, with a median of two dissected SNs. In the Z1071 study, use of a dual method and identification of three or more SNs improved the FNR to 10.8% and 12.8%, respectively, from an FNR of 32% with detection of a single SN. In the SENTINA study, the FNR was reduced to 9.6% when two or more SNs were removed and to 8.6% when the dual method was used to identify SNs. Similarly, the SN FNAC study,<sup>39</sup> where patients with pre-NACT biopsy-proven axillary nodes were considered for SNB after NACT, reported an overall FNR of 13% (excluding isolated tumor cells [ITCs]), which was reduced to < 5% with removal of three or more SNs. In addition, identification of ITCs reduced the FNR further to 4.6%, although the clinical significance of this is unclear.<sup>40</sup>

In our LAS study, as summarized in Table 6, we could identify three or more sampled LNs in 676 (91.3%) of 740 patients, with an FNR that was further reduced to 8.8% when three or more nodes were sampled with LAS, with sensitivity of 83% and a high NPV of 94.4%. These results were by far superior to those obtained when three or more LNs were identified by SNB with palpable nodes (FNR, 18.3%; sensitivity, 67.7%; NPV, 91.0%).

TNBC and HER2-positive disease<sup>41</sup> have aggressive biologic behavior, but they may show excellent response to systemic chemotherapy and targeted therapy, with complete response in primary and axillary nodal disease clinically. ALND therefore seems to be unnecessary in such patients if the decision is based on prechemotherapy positive axilla, but it may represent a lost opportunity to treat the axilla conservatively if all nodes respond well to chemotherapy. One must keep in mind, however, that with any high FNR on SNB postchemotherapy, the relatively poor biology involves a relatively higher risk of relapse if disease is left behind in the axilla. SNB and targeted identification of axillary disease work well in patients with early cancer and a healthy lymphatic system, but they become unreliable in those with chemotherapy-induced negative axilla.

With regard to a subset analysis of tumor biology and LAS in this study, there was no apparent significant direct impact of tumor biology on the FNR in LAS. The postchemotherapy FNR by LAS was 12.6% in women IHC-proven HER2-positive disease, 9.1% in women with HER2-negative or -equivocal disease, and 10.6% in those with TNBC. However, as cautioned earlier, outcome can be affected by

tumor biology, and this fact should be kept in mind if limited axillary intervention is being implemented based on LAS or SNB (plus palpable nodes).

Our study clearly demonstrates the superiority and ease of axillary sampling of lower axillary nodes compared with targeted SNB, with a lower FNR meeting the preset limits, and thus holds promise for replacing the relatively unreliable SNB procedure in this subset of patients evaluated after chemotherapy. The simplicity of the intervention also makes it widely applicable in other centers without resulting in undue risk or morbidity. A prospective randomized study could further prove long-term benefits and harms in relation to outcome and quality of life.

In conclusion, in large and locally advanced breast cancers, NACT effectively reduced the primary tumor from 5 to 2 cm, with residual axillary disease burden reduced from 71% to 38.6%. Targeted SNB alone (using blue dye- and technetium-99-labeled radiocolloid) in these relatively larger tumors after chemotherapy had a high FNR of 31.6% (upper limit of 95% CI, 36.6), with an NPV of 81.3%.

Using the LAS technique of sampling the palpable nodes and axillary fat defined by anatomic boundaries improved the FNR to 9.9%, with a one-sided 95% CI upper limit of 12.8 ( $P < .001$ ) and a better NPV of 94.0% in these larger tumors, and this can be considered a suitable alternative in

countries with limited resources where nuclear medicine facilities or gamma probe procedures are not available. In the subset of patients where SNB included palpable nodes, false negativity was still high at 19.7%, with a 95% CI upper limit of 24 ( $P < .001$ ).

LAS is clearly superior to SNB with regard to identification rate, FNR, and NPV in predicting node-negative axilla post-NACT, with a  $< 10\%$  chance of leaving residual disease. It also seems that the FNR with LAS is not truly affected by biology of disease, and the LAS technique can therefore be universally applied. Also, identification of three or more LNs by LAS lowered the FNR still further to 8.8%; this makes it a more reliable technique, and therefore, we recommend that three or more LNs be removed and confirmed (in frozen section).

We still need long-term follow-up data on the safety of axillary conservation post-NACT in locally advanced cancers, especially in developing countries, where patients tend to have heavier disease burden with poorer biology, compared with patients in the West who receive NACT who tend to have smaller tumors with better biology. Until such time, complete axillary clearance may be advisable for women with tumors with poorer biology. In others, LAS may be an option, after careful consideration, for avoiding unnecessary axillary clearance if nodes are negative on sampling after chemotherapy.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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