INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for the use of sentinel node biopsy during surgical resection of early stage breast cancer. The standard approach to the surgical evaluation of breast cancer has been to do an axillary lymph node dissection, but this procedure is associated with a significant risk for lifelong symptoms in the ipsilateral arm including lymphedema, pain, neuropathy, and decreased range of motion. Despite the lack of clinical trial evidence, the trend among surgeons has been to remove the first lymph nodes draining the breast and only performing axillary node dissection if the so-called sentinel node contains metastatic breast cancer. Several large randomized trials have recently published their primary results.

BACKGROUND

Breast Cancer

Cancer of the breast is the most common form of cancer in women. Every American woman is estimated to have a one in eight chance of developing breast cancer at some time during her life. In 2012, there will be an estimated 226,870 new cases of invasive breast cancer in the United States and an estimated 39,510 deaths from this cancer.¹ This represents approximately 29% of all new cancer
cases and 14% of all cancer deaths in women.¹

The staging system of the American Joint Committee on Cancer (AJCC)² defines Stage I, II, and IIIA invasive breast cancer as early stage breast cancer. In the TNM (Tumor Node Metastasis) staging system for breast cancer, stage T1 refers to carcinomas 2.0 cm or less in greatest dimension; stage T2 refers to tumors more than 2.0 cm, but not more than 5.0 cm in greatest dimension; stage T3, to tumors more than 5.0 cm in greatest dimension; and stage T4, to tumors of any size that have direct extension to chest wall or skin. Stage N0 refers to tumors without regional lymph node metastasis and N1 refers to tumors with ipsilateral metastases to mobile level I or II axillary lymph nodes. N2 refers to tumors with ipsilateral metastases to fixed or matted level I or II axillary lymph nodes. N3 refers to tumors with ipsilateral metastases to level III axillary lymph nodes, internal mammary lymph nodes or supraclavicular lymph nodes. M0 refers to tumors without distant metastases and M1 to distant metastases. The stages of breast cancer are defined below.

- **Stage 0** - Carcinoma in situ
- **Stage I** – T1 N0.
- **Stage IIA** – T1 N1 or T2 N0
- **Stage IIB** – T2 N1, or T3 N0.
- **Stage IIIA** – T1-2 N2 or T3 N1-2
- **Stage IIIB** – T4 N0-2
- **Stage IIIC** – Any T N3
- **Stage IV** – Any T, Any N M1

**Treatment of early stage breast cancer**

Nodal status used to be one of the most important prognostic factors in breast
cancer. For example, the five year survival for localized breast cancer is 99%, but for patients with positive lymph nodes it is only 84%. Lymph node status is also an important determinant of the treatment offered for breast cancer. In almost all cases, treating physicians will offer systemic chemotherapy to patients with positive lymph nodes, but not to patients with small, node negative cancers with other favorable tumor characteristics.

Staging and risk assessment have important limitations. Patients with the same stage breast cancer can have markedly different responses to therapy and long-term outcomes. The majority of women with hormone receptor positive, node negative breast cancer have no evidence of breast cancer recurrence after ten years of follow-up, even if they are classified in a higher risk group using standard clinical measurements. In the NSABP-20, a randomized trial of women with estrogen receptor positive, lymph node negative breast cancer less than five cm in diameter, 83% of women treated with tamoxifen alone were disease free at ten years. However, many patients with early stage breast cancer are treated with chemotherapy in the United States.

**Sentinel Lymph Node Biopsy (SLNB)**

Traditionally, axillary lymph node dissection (AD) is done as part of the standard treatment for early stage breast cancer. Identifying the number and location of axillary lymph nodes that contain metastatic disease provides important staging information and influences treatment decisions as described above. In addition, removal of the affected lymph nodes may help to reduce the risk for recurrence of breast cancer in the axilla and to reduce the risk for later metastatic recurrence.

However, axillary lymph node dissection can cause significant morbidity. The
disruption of the lymphatic system in the axilla can cause significant lymphedema in the ipsilateral arm. In addition, women may experience long-term sensory loss, pain, and a decrease in the range of motion of the affected arm. The majority of women with early breast cancer do not have lymph node involvement; so axillary lymph node dissection puts them at risk for complications with no benefits.

Surgeons developed sentinel lymph node biopsy to identify women who may not need further axillary node dissection.\textsuperscript{9,10} Theoretically, tumor cells should travel along lymph channels near the primary tumor and spread to one or more proximal lymph nodes before spreading to additional lymph nodes deeper in the drainage system. The sentinel node is any node that directly drains the primary tumor. Thus, there can be more than one sentinel node. If the first or sentinel lymph nodes do not contain tumor, then theoretically the remainder of the lymph system should be free from cancer and complete axillary lymph node dissection can be avoided.

Surgeons use two classes of tracers to identify the sentinel lymph nodes: blue dyes and radioactive colloid. One or both of these are injected either around the tumor or in the subareolar region of the affected breast.\textsuperscript{9,10} The tracers travel along the lymphatic channels draining the breast to the axilla enabling the surgeon to identify the sentinel node. The tracer should not be injected directly into the tumor or into the tumor cavity if lumpectomy has already been performed because the lymphatic system may be disrupted or occluded in those locations. Comparative studies suggest that sentinel nodes are identified more frequently with radioactive colloid than with blue dye and that the combination of both agents is associated with a higher sensitivity for the detection of nodes with metastatic disease.\textsuperscript{11-14}

Isosulfan blue dye is the recommended dye. The surgeon injects about five cc of dye at the time of surgery.\textsuperscript{9,10} The surgeon then massages the breast for about five minutes to dilate the lymphatic ducts and enhance drainage of the dye into the axilla.
A small inferior incision is made in the axilla and the region is carefully inspected for blue lymphatic vessels leading to blue lymph nodes. The most blue node and the node closest to the tumor are usually removed. Finally, the axilla is inspected and palpated for additional suspicious lymph nodes and those are removed.

A number of different radioactive colloids have been studied. In the United States, Technetium-labeled sulfur is most commonly used. In Europe, Technetium-labeled albumin is commonly used; Technetium-labeled antimony is also used. Prior to skin incision, a hand-held gamma probe is used to locate radioactively “hot” spots in the axilla. During surgery, an incision is made at the hot spot and the gamma probe guides the surgeon to the sentinel node or nodes.

Early studies found that these techniques identify a sentinel node in between 92% and 98% of patients and there is 97% to 100% concordance between the SLNB and AD. The primary concern with SLNB is false negatives: patients that have no metastases found on SLNB, but do have positive lymph nodes on AD. These patients may be at higher risk for local recurrence and a meta-analysis performed by the Early Breast Cancer Trialist’s Collaborative Group has documented that better local control eventually leads to fewer deaths from breast cancer. A systematic review of 69 studies performed in 2004 as part of guideline development for ASCO found that the false negative rate (1-sensitivity) ranges from 0% to 15%. More importantly, observational studies have reported very low rates of axillary recurrence following a negative sentinel lymph node biopsy.

The detection of sentinel nodes is a technically difficult procedure with a significant learning curve. The American Society of Breast Surgeons has published guidelines on credentialing criteria and recommend a minimum of 20 procedures either proctored or with axillary dissection prior to performing SLNB alone.
TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

Sentinel lymph node biopsy (SLNB) is a procedure and therefore not under the purview of the U.S. Food and Drug Administration (FDA). However, equipment including instrumentation, assays, etc. used to perform SLNB are under FDA oversight

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Embase, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “sentinel lymph node” OR “sentinel node” AND “breast neoplasms” OR “breast cancer.” The search was performed for the period from 1945 through September 2012. The bibliographies of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. We included all randomized trials in women with invasive breast cancer that compared sentinel lymph node biopsy to axillary lymph node dissection.

The search identified 587 potentially relevant studies (Figure 1). After elimination of duplicate and non-relevant references the search identified two systematic reviews\textsuperscript{23,24} and 37 articles describing ten randomized trials.\textsuperscript{12,25-60}
Figure 1: Selection of studies for inclusion in review

587 potentially relevant references screened

115 abstracts for assessment

56 studies for full text review

37 references on 10 randomized trials included in the assessment

194 duplicate citations excluded
278 excluded: not randomized; reviews, abstracts only; other interventions

59 studies excluded (Editorials, reviews, abstracts, no clinical outcomes)

17 studies excluded: no primary data, reviews

Level of Evidence: 1 and 2
TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

The two most important outcomes in cancer are overall survival (OS) and disease-free survival (DFS). Because early stage breast cancer has such a long natural history and the majority of women do well, large randomized trials with long
follow-up are needed to demonstrate the equivalence of these outcomes in patients managed with SLNB to patients managed with AD. One of the potential early indicators of worse outcome with SLNB would be recurrence in the ipsilateral axilla, so the rate of locoregional recurrence is also an important outcome. Most locoregional recurrence occurs in the first five years after diagnosis, but DFS requires up to eight years follow-up to assess differences and ten to fifteen year follow-up is needed for OS. Finally, the primary reason for doing SLNB is to reduce the morbidity associated with AD, so important secondary outcomes are the rates of lymphedema, pain, neuropathy, and reduced range of motion in the ipsilateral arm.

Randomized controlled trials

The initial results of ten randomized trials have been published. The methodologic quality of the studies is summarized in Table 1 and the characteristics of the studies are summarized in Table 2. The primary benefits are summarized in Table 3 and the harms in Table 4. The individual studies are described below.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country/Centers</th>
<th>Randomization</th>
<th>Allocation concealment</th>
<th>Groups comparable</th>
<th>Blinding</th>
<th>Follow-up &gt; 80%</th>
<th>Intention-to-treat analysis</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purushotham 2005</td>
<td>UK 3 Centers</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Poor</td>
</tr>
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<td>UK</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
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<td>Australia / NZ</td>
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<td>NR</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Helms 2008</td>
<td>Italy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Canavase 2009</td>
<td>Italy Single Center</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Gill 2009</td>
<td>Australia / NZ</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Vero</td>
<td>Italy Multicenter</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Fougo 2011</td>
<td>Portugal Single Center</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Giuliano 2011</td>
<td>USA/ACOSOG-Z0011</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Krag 2010, Weaver 2011</td>
<td>US, Canada</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
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</table>
Table 2: Characteristics of the Randomized Trials Comparing Sentinel Lymph Node Biopsy to Axillary Dissection

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Centers</th>
<th>SLNB Technique</th>
<th>SLN Evaluation</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Enroll Period</th>
<th>FU (years)</th>
<th>Age, Tumor Size</th>
<th>Primary Outcome</th>
<th>Secondary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purushotham 2005</td>
<td>UK 3 Centers</td>
<td>49</td>
<td>Blue dye + Albumin*</td>
<td>H&amp;E + cytokeratin IHC</td>
<td>IBC ≤ 3 cm</td>
<td>CN-</td>
<td>1999-2003</td>
<td>1</td>
<td>1.6 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goyal 2007</td>
<td>UK 3 Centers</td>
<td>28, 29, 31, 37, 47</td>
<td>Blue dye + Albumin*</td>
<td>H&amp;E</td>
<td>IBC any size</td>
<td>Age &lt; 80 y</td>
<td>1999-2003</td>
<td>1.5</td>
<td>58</td>
<td>75% ≤ 2 cm</td>
<td></td>
</tr>
<tr>
<td>Helms 2008</td>
<td>Germany</td>
<td>181</td>
<td>Blue dye</td>
<td>H&amp;E</td>
<td>IBC &lt; 2.5 cm</td>
<td>Age ≥ 70-75</td>
<td>2000-2002</td>
<td>0.9</td>
<td>58</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Zavagno 2008</td>
<td>Italy 18 Centers</td>
<td>30, 58, 60</td>
<td>Albumin*</td>
<td>H&amp;E + cytokeratin IHC</td>
<td>IBC ≤ 3 cm</td>
<td>Age ≤ 80 y</td>
<td>1999-2004</td>
<td>4.6</td>
<td>Median 50-69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canavase 2009</td>
<td>Italy Single Center</td>
<td>27</td>
<td>Blue dye + Albumin*</td>
<td>H&amp;E + cytokeratin IHC</td>
<td>IBC &lt; 3 cm</td>
<td>Multifocal</td>
<td>1998-2001</td>
<td>5.5</td>
<td>58</td>
<td>81% T1</td>
<td>DFS</td>
</tr>
<tr>
<td>Gill 2009</td>
<td>Australia / NZ</td>
<td>26, 33, 34, 50, 52, 57</td>
<td>Blue dye</td>
<td>H&amp;E + cytokeratin IHC</td>
<td>IBC &lt; 3 cm</td>
<td>Multifocal</td>
<td>2001-2005</td>
<td>1</td>
<td>Median 50-69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verolesi 2010</td>
<td>Italy Multicenter</td>
<td>532</td>
<td>Blue dye</td>
<td>H&amp;E + cytokeratin IHC</td>
<td>IBC ≤ 2 cm</td>
<td>Age 40-75 y</td>
<td>1998-1999</td>
<td>7.9</td>
<td>56</td>
<td>Median 1.1-1.5 cm</td>
<td></td>
</tr>
<tr>
<td>Fougo 2011</td>
<td>Portugal Single Center</td>
<td>166</td>
<td>Blue dye</td>
<td>H&amp;E + cytokeratin IHC</td>
<td>IBC ≤ 3 cm</td>
<td>Age 18-80 y, Prior Tx</td>
<td>2001-2003</td>
<td>6.0</td>
<td>54</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Giuliano 2011</td>
<td>USA</td>
<td>891</td>
<td>Blue dye + Antimony*</td>
<td>H&amp;E + cytokeratin IHC</td>
<td>IBC &lt; 3 cm</td>
<td>Age ≥ 18 y</td>
<td>1999-2004</td>
<td>6.3</td>
<td>Median 50-69</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Colloid radiolabeled with technetium.
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Enrollment period</th>
<th>FU (years)</th>
<th>Age, years</th>
<th>Tumor size (mm)</th>
<th>Primary outcome</th>
<th>Adjunct technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOSOG-Z0011</td>
<td>Extranodal nodes, blue dye + Sulfur* H&amp;E</td>
<td>Age ≥ 60 y</td>
<td>1999-2004</td>
<td>8.0</td>
<td>80</td>
<td>2.0 cm</td>
<td>Extracapsular spread</td>
<td>N</td>
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<tr>
<td>Krag 2010; Weaver 2011</td>
<td>IBC any size, Age ≥ 18</td>
<td>Prior BC Tx</td>
<td>1999-2004</td>
<td>8.0</td>
<td>80</td>
<td>2.0 cm</td>
<td>Extracapsular spread</td>
<td>N</td>
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<tr>
<td>NSABP-B32</td>
<td>IBC any size, Age ≥ 18</td>
<td>Prior BC Tx</td>
<td>1999-2004</td>
<td>8.0</td>
<td>80</td>
<td>2.0 cm</td>
<td>Extracapsular spread</td>
<td>N</td>
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<tr>
<td>Study</td>
<td>Location</td>
<td>Centers</td>
<td>SLNB</td>
<td>AD</td>
<td>N</td>
<td>Success</td>
<td>SLN</td>
<td>Overall</td>
</tr>
<tr>
<td>-------</td>
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<td>---------</td>
</tr>
<tr>
<td>Purushotham 2005</td>
<td>UK 3 Centers</td>
<td>SLNB</td>
<td>26</td>
<td>1</td>
<td>7</td>
<td>26</td>
<td>1</td>
<td>7</td>
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<tr>
<td>Goy et al. 2007</td>
<td>UK ALMANAC (39)</td>
<td>SLNB</td>
<td>16</td>
<td>0</td>
<td>1</td>
<td>16</td>
<td>0</td>
<td>1</td>
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<td>Helms 2008</td>
<td>Germany KiSS</td>
<td>SLNB</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Zavagno 2008</td>
<td>Italy 18 Centers</td>
<td>SLNB</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>15</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Canavase 2009</td>
<td>Italy Single Center</td>
<td>SLNB</td>
<td>29</td>
<td>0</td>
<td>1</td>
<td>29</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gill 2009</td>
<td>Australia / NZ SNAC</td>
<td>SLNB</td>
<td>30</td>
<td>0</td>
<td>1</td>
<td>30</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Verolesi 2010</td>
<td>Italy Multicenter</td>
<td>SLNB</td>
<td>26</td>
<td>0</td>
<td>1</td>
<td>26</td>
<td>0</td>
<td>1</td>
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</tbody>
</table>

Table 3: Primary Outcomes in the Randomized Trials Comparing Sentinel Lymph Node Biopsy to Axillary Dissection
<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>N</th>
<th>Success</th>
<th>SLNB</th>
<th>Sensitivity</th>
<th>Nodes removed</th>
<th>Pathologically node positive</th>
<th>Local recurrence</th>
<th>Disease free survival</th>
<th>Overall survival</th>
<th>Location</th>
<th>Members</th>
<th>Race</th>
<th>AD</th>
<th>Study Group</th>
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<tbody>
<tr>
<td>&quot;Portugal Single Center&quot;</td>
<td>Giuliano 2011</td>
<td>49</td>
<td>NR</td>
<td>0%</td>
<td>96.4%</td>
<td>88.6%</td>
<td>99%</td>
<td>98%</td>
<td>3.1%</td>
<td>90%</td>
<td>100%</td>
<td>3.1%</td>
<td>8 y</td>
<td>94%</td>
<td>0.006</td>
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<tr>
<td>&quot;USA ACOSOG-Z0011&quot;</td>
<td>Krag 2010, Weaver</td>
<td>446</td>
<td>100%</td>
<td>445</td>
<td>100%</td>
<td>100%</td>
<td>2.8</td>
<td>5 y</td>
<td>3.1%</td>
<td>97%</td>
<td>97%</td>
<td>2.8</td>
<td>5 y</td>
<td>94%</td>
<td>0.11</td>
</tr>
<tr>
<td>&quot;US, Canada NSABP-B32&quot;</td>
<td>Giuliano 2011, Z9115</td>
<td>2804</td>
<td>97%</td>
<td>2807</td>
<td>97%</td>
<td>97%</td>
<td>90%</td>
<td>2.8</td>
<td>26%</td>
<td>8 y</td>
<td>28%</td>
<td>26%</td>
<td>3.1%</td>
<td>8 y</td>
<td>83.9%</td>
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<td>&quot;Center Portugal Single&quot;</td>
<td>&quot;Krag 2010, Weaver&quot;</td>
<td>446</td>
<td>49</td>
<td>AD</td>
<td>49</td>
<td>49</td>
<td>49</td>
<td>49</td>
<td>49</td>
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<td>49</td>
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</tbody>
</table>

Note: Table details specific data regarding study outcomes, including success rates, sensitivity, and survival statistics.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Group</th>
<th>N</th>
<th>Lymphedema</th>
<th>Seroma</th>
<th>Sensory Neuropathy</th>
<th>Shoulder ROM</th>
<th>Pain</th>
<th>Quality of Life</th>
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</thead>
<tbody>
<tr>
<td>Purushotham 2005</td>
<td>UK 3 Centers</td>
<td>SLNB vs. AD</td>
<td>143</td>
<td>0.36 (0.2-0.9) p=0.03</td>
<td>14%</td>
<td>1%</td>
<td>66%</td>
<td>1%</td>
<td>NR</td>
</tr>
<tr>
<td>Goyal 2007</td>
<td>UK 3 Centers</td>
<td>SLNB vs. AD</td>
<td>516</td>
<td>0.48 (0.3-0.8) p=0.01</td>
<td>11%</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
<td>NR</td>
</tr>
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<td>Helms 2008</td>
<td>Germany</td>
<td>SLNB vs. AD</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Zavagno 2008</td>
<td>Italy 18 Centers</td>
<td>SLNB vs. AD</td>
<td>NR</td>
<td>OR 0.48 (0.3-0.8) p&lt;0.001 for arm volume favoring SLNB</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Canavase 2009</td>
<td>Italy Single Center</td>
<td>SLNB vs. AD</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gill 2009</td>
<td>Australia / NZ</td>
<td>SLNB vs. AD</td>
<td>NR</td>
<td>2.8%</td>
<td>0.001</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
<td>NR</td>
</tr>
<tr>
<td>Vero</td>
<td>Italy Multicenter</td>
<td>SLNB vs. AD</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>NR</td>
</tr>
<tr>
<td>Fougo 2011</td>
<td>Portugal Single Center</td>
<td>SLNB vs. AD</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Table 4: Quality of Life Outcomes in The Randomized Trials Comparing Sentinel Lymph Node Biopsy to Axillary Dissection
<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>N</th>
<th>Lymphedema</th>
<th>Seroma</th>
<th>Sensory Neuropathy</th>
<th>Shoulder ROM</th>
<th>Pain</th>
<th>Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giuliano 2011</td>
<td>NA</td>
<td>445</td>
<td>6%</td>
<td>0.001</td>
<td>14%</td>
<td>0.001</td>
<td>19%</td>
<td>0.001</td>
</tr>
<tr>
<td>ACOSOG-Z0011</td>
<td>USA, Canada</td>
<td>2010, Weaver</td>
<td>2804</td>
<td>8%</td>
<td>0.5y</td>
<td>16%</td>
<td>0.001</td>
<td>39%</td>
</tr>
</tbody>
</table>

**Study Group**

- **Quality of Life**
  - No significant difference after 6 months
  - Significant early, but no difference at 1 year

**Notes**

- **SLNB**
- **AD**
- **NSABP-B32**
- **NR**
- **US, Canada**
- **ACOSOG-Z0011**
- **USA**
- **Krag 2010**, Weaver

**Key**

- **SLNB**
- **AD**
- **NR**
- **US, Canada**
- **ACOSOG-Z0011**
- **USA**
- **Krag 2010**, Weaver

**Abbreviations**

- **SLNB**: Sentinel Lymph Node Biopsy
- **AD**: Axillary Dissection
- **NR**: Not Reported
- **USA**: United States of America
- **Canada**
- **ACOSOG-Z0011**: American College of Surgeons Oncology Group Z0011

**Table Columns**

- Months
- Pain
- Shoulder ROM
- Sensory Neuropathy
- Lymphedema
- Quality of Life
- p-value

**Table Rows**

- Giuliano 2011
- ACOSOG-Z0011
- SLNB
- AD
- NR
**Summarizing the trials**

Table 1 summarizes the quality of the published randomized trials. All of the studies suffer from lack of blinding to randomization assignment. This could lead to differences in co-interventions, such as the use of radiation therapy or the use of adjuvant chemotherapy, which may impact breast cancer mortality. It also could impact the patient’s self-assessment of ipsilateral arm symptoms and quality of life. Overall the quality of the trials was fair.

Table 2 highlights the heterogeneity of the patient populations studied, the techniques used for the identification of the sentinel lymph node, and the histopathology used to identify cancer in the sentinel nodes. Most of the trials included patients with IBC ≤ 3 cm with clinically negative axillary lymph nodes. Two of the trials included only patients with smaller tumors and two of the trials enrolled patients with tumors of any size. The studies generally excluded patients with multifocal disease and prior breast cancer treatment because of the potential for poor localization of sentinel nodes and pregnant women due to potential toxicity from both the dye and the radiation. Most of the studies began enrollment in 1999 or 2000, but only half of the studies have reported outcomes through five or more years.

The majority of the trials used both blue dye and a radioactive colloid to identify the sentinel nodes, but two of the trials only used radiolabeled albumin colloid. Of note (see Table 3), the two trials that did not use blue dye successfully identified sentinel nodes in about the same proportion of subjects as the other studies, but the sensitivity of the sentinel nodes for detection of metastatic disease found with axillary dissection was low in the GIVOM study. In addition, many of the studies used immunohistochemistry (IHC) staining for cytokeratin to increase the sensitivity for metastatic disease when examining pathologic slides. However, the clinical
importance of metastatic disease identified solely using IHC remains controversial. Most of the larger, commonly cited studies only classified sentinel nodes as positive or negative for metastatic breast cancer based on hematoxylin and eosin (H&E) stains including the NSABP-B32 study, the ACOSOG-Z0011 study, and the ALMANAC study.

There are two other differences in the design of the trials that are not highlighted in Table 2. First, one study randomized patients to either axillary dissection without prior SLNB or to SLNB with AD for subjects with a positive sentinel node. This design does not allow for the calculation of the sensitivity of SLNB or the false positive rate (1-sensitivity) - there is no group of subjects that randomly was chosen to receive both AD and SLNB. Another study (ACOSOG Z0011) performed SLNB on all potential subjects, but only randomized patients with one or two positive sentinel lymph nodes to AD or no AD. As opposed to the other trials that examined the utility of AD in patients with negative sentinel lymph nodes, the primary research question in the Z0011 trial was whether AD improved patient outcomes in sentinel node positive patients. Because all of the subjects in the trial were node positive, they would be expected to have a higher incidence of recurrence and a lower DFS than a study population that included both sentinel node negative and positive patients. Finally, most of the trials compared the outcomes of the SLNB group to the AD group as randomized. However, the NSABP B32 trial, which was by far the largest and highest quality study, directly compared the outcomes of the subjects with negative sentinel nodes in the SNLB and AD groups rather than including subjects with positive sentinel nodes in their analyses. Thus, they were evaluating whether the outcomes of patients with negative sentinel nodes without AD were equivalent to those of patients with negative sentinel nodes treated with AD. Because all of the reported outcomes for subjects in the NSABP B32 trial were in sentinel node negative patients, their recurrence rates should be lower than those observed in studies including subjects with both positive and sentinel nodes.
Table 3 summarizes the primary outcomes of the study. Surgeons successfully identified sentinel nodes in 94% to 100% of the study subjects in all studies as had been described in prior observational studies. However, the sensitivity varied significantly between studies. Two of the Italian studies had unacceptably high false negative rates (sensitivity < 90%). In the GIVOM trial, the sensitivity of SLNB was 83%. This may explain the higher locoregional recurrence in this study (4.6% in SLNB group versus 0.9% in AD group, p not reported), although this did not result in significant differences in five year disease free survival or overall survival. In the second Italian trial, the 77% sensitivity was not associated with a trend towards greater locoregional recurrence or lower DFS, though the follow-up may have been too short at one year.

As expected, the number of lymph nodes removed was much lower with SLNB than with AD (approximately 2 versus 16). About 30% of the randomized subjects had positive lymph nodes by SLNB or AD. There were no significant differences in DFS or OS in any of the studies. Trends towards better outcomes favored the SLNB group as often as they favored the AD group. See the Tables and the discussion of the larger individual trials below for more detail.

Table 4 summarizes the outcomes in the arm ipsilateral to the primary breast cancer and the overall quality of life outcomes. Unfortunately, there are no standard objective or subjective assessments for lymphedema, neuropathy associated with axillary dissection, shoulder range of motion or function, and pain. Each study used different measures. However the trends consistently favored SLNB for all ipsilateral arm outcomes. For example, in the NSABP-B32 trial, 8% of the SLNB group reported lymphedema at the 3-year follow-up compared to 14% of the AD group (p<0.001). Short term surgical outcomes such as seroma formation, wound infection, and hospital length of stay were all significantly shorter in the SLNB group. This likely explains why quality of life outcomes were better in the SLNB group over the
first three to six months of follow-up, although the differences tended to disappear by one year. Many of the self-reported outcomes could represent measurement bias because of lack of blinding – patients randomized to the SLNB group may have expected better outcomes. However many of the studies also estimated arm volume by measuring arm circumference and measures shoulder range of motion as objective outcomes supporting the subjective self-reported outcomes.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B32

The NSABP B32 study randomly assigned 5,611 patients to SLNB with AD only if the sentinel nodes were positive (SLNB group) or to SLNB plus AD (AD group).\textsuperscript{12,22,25,40,42-45,56} The study was designed as an equivalence trial with overall survival in subjects with negative sentinel nodes pre-specified as the primary outcome. It was powered to detect a difference in overall survival at five years of follow-up with a difference of 2% or less considered equivalent. Patients with any size tumor were eligible, but the large majority (85%) had tumors ≤ 2 cm. At the time of the primary analysis, the median follow-up was eight years and all randomized patients had more than five years of follow-up.\textsuperscript{42} There were 2,011 patients in the SLNB group with negative sentinel nodes and 1,975 patients in the AD group with negative sentinel nodes. At five years, the OS was 95.0% in the SLNB group and 96.4% in the AD group (p=0.12). Similarly the five-year DFS was 88.6% in the SLNB group and 89.0% in the AD group (p=NR). At eight years, the OS was 90.3% and 91.8% in the two groups and the DFS was 81.5% and 82.4%. The number of locoregional recurrences were nearly identical during follow-up: 63 (3.1%) in the SLNB group and 62 (3.1%) in the AD group. There was a non-significant trend towards more recurrences in the SLNB group (14 recurrences versus 8 recurrences, p = 0.22). There were allergic reactions reported by 46 patients (0.8%) primarily due
to the blue dye.

The NSABP B32 trial measured arm volume every six months for three years. Arm volume differences of greater than 10% were still present in 7.5% of the SLNB group and 14.3% of the AD group (p<0.001). Shoulder abduction deficits of greater than 10% were most common one week following surgery (41% SLNB group, 75% AD group, p<0.001), but were still significantly different when last assessed at six months (5.7% versus 9.0%, p < 0.001). Self-reported numbness and tingling were less common in the SLNB group at all time points through three years (p<0.001). A subgroup of 749 patients enrolled in the trial completed a series of questionnaires on arm symptoms, activity limitations, and quality of life at baseline, one and three weeks, and then every six months through three years. There were significant differences in favor of the SLNB group in self-reported restrictions in occupational activities, recreational activities, and overall quality of life from one week to six months after surgery, but the scores were nearly identical in the two groups at twelve months and later.

This trial provides the strongest evidence for the use of SNLB in patients with early stage breast cancer who do not appear to have lymph node metastases on clinical examination. It is a large randomized trial administered by an organization with a long track record in performing high quality randomized trials. Follow-up was 99.9% complete through a median of eight years. There were non-significant trends towards lower disease free and overall survival at five and eight years of follow-up. The follow-up is long enough and the trial large enough to detect clinically important differences in disease free survival: at eight years the absolute difference in disease free survival was less than 1%. There was also less surgical morbidity in the SLNB group and their quality of life was better during the six months following surgery. The lack of blinding may have contributed to some of the difference in self-reported outcomes, but is unlikely to explain the objective measures of arm volume and
shoulder mobility.

The Veronesi et al Italian Study\textsuperscript{53-55}

The other trial with long follow-up (median 7.9 years) published their 10-year estimates for DFS and OS in 2010.\textsuperscript{55} As in the NSABP B32, the investigators randomized 532 patients with invasive breast cancers $\leq 2$cm to either SLNB with AD only if the sentinel nodes were positive (SLNB group) or to SLNB plus AD (AD group). However, the investigators in this Italian study compared all patients as randomized, not just the patients with negative sentinel nodes. The 10-year locoregional recurrence rate was 2.2\% in both arms. The trends in 10-year DFS (89.9\% versus 88.8\%, p=0.52) and 10-year OS (93.5\% versus 89.7\%, p=0.15) both favored the SLNB group.

The American College of Surgeons Oncology Group (ACOSOG) Z0011 Trial\textsuperscript{35,36,46}

The ACOSOG Z0011 trial complements the NSABP B32 trial. Investigators noted that observational studies documented that the sentinel nodes were the only positive lymph nodes following axillary dissection in about half of patients and that their was excellent local control in patients with early stage breast cancer and one or two positive sentinel nodes.\textsuperscript{9,61} In Z0011, the investigators randomized 821 patients with T1 or T2 invasive breast cancer, no palpable adenopathy, and one or two positive sentinel lymph nodes to either no further nodal dissection (SLNB group) or standard axillary dissection (AD group). All patients underwent lumpectomy, tangential whole-breast irradiation, and appropriate systemic therapy. The trial was designed to enroll 1,900 women in order to demonstrate equivalence in overall survival, but closed early due to lower than expected mortality in both groups of the
study. After a median follow-up of 6.3 years, the trends in five year DFS (83.9% versus 82.2%, p NR) and five year OS (92.5% versus 91.8%, p NR) both favored the SLNB group. Locoregional recurrence was also lower in the SLNB group (1.6% versus 3.1%, p=0.11). The hazard ratio (HR) for OS was 0.79 (95% confidence interval 0.56 to 1.10). The HR for DFS, which is likely more relevant after this relatively short follow-up period, was 0.82 (95% confidence interval 0.58 to 1.17).

As expected, surgical morbidity was lower in the SLNB group. These included wound infection at 30 days (3% versus 8%, p=0.0016), axillary seromas (6% versus 14%, p=0.001), paresthesias at one year (9% versus 39%, p<0.001), lymphedema at one year by self report (6% versus 19%, p<0.001), and lymphedema at one year by arm measurements (6% versus 11%, p=0.079).

**Harms**

The primary harms specific to SLNB include allergic reactions to the blue dye, radiation exposure from the radiolabeled colloid, and false negatives. False negatives may lead to understaging and undertreatment of women with node positive breast cancer that would have been discovered on standard axillary lymph node dissection. This would potentially lead to higher rates of locoregional recurrence and lower rates of disease-free and overall survival. Those outcomes were described earlier in the assessment. The radiation dose is negligible in comparison with the radiation therapy used for breast cancer following lumpectomy. Allergic reactions are potentially serious, but relatively uncommon. As documented above in the B32 trial, they occur in less than 1% of all women receiving blue dye for sentinel node mapping. Of the 46 allergic reactions documented in the B32 trial only 10 were grade 4 reactions and 3 were grade 3.
Other systematic reviews and meta-analyses.

The search identified two relatively recent systematic reviews and meta-analyses. The first, by Kell et al, identified seven randomized trials including 9,608 patients. They found no difference in the rate of axillary node positivity between SLNB and AD (OR 1.00, 95% CI 0.95 to 1.17, p=0.96). However, there were significantly fewer morbidities with SLNB including infection (OR 0.58, 95% CI 0.42-0.80, p=0.001), seroma (OR 0.40, 95% CI 0.31-0.51, p=0.007), arm swelling (OR 0.30, 95% CI 0.14-0.66, p=0.003), and numbness (OR 0.24, 95% CI 0.10-0.59, p=0.002).

The second meta-analysis, by Wang et al, focused more on OS, DFS, and locoregional recurrence. There were no significant differences between SLNB and AD in OS (HR 1.07, 95% CI 0.90-1.27), DFS (HR 1.00, 95% CI 0.88-1.14), or regional lymph node recurrence (OR 1.65, 95% CI 0.77-3.6). The trend in regional lymph node recurrence was concerning, but there was also significant heterogeneity in meta-analysis of this outcome. There was minimal, non-significant heterogeneity for OS and DFS. They also noted unequivocally fewer morbidities following SLNB including lymphedema, paresthesias, and seroma formation.

Summary

There are ten published randomized trials comparing SLNB to AD in early stage breast cancer. Six of the ten have published their five to ten year outcome data, which should be long enough to see any important trends in DFS, though perhaps not in OS. There were no significant differences in DFS or OS between the two groups in any of the studies with some studies showing trends favoring SLNB and others favoring AD. These differences likely represent random variation. The
summary estimates from the published meta-analyses also suggest no important differences in DFS between SLNB and AD. These data are still somewhat immature for a disease like early stage breast cancer, which has a long natural history. At least one of the four studies that has not published their long-term outcomes data has presented their data at an international meeting. Additional follow-up from all of the randomized trials will help to better delineate the role of SLNB. The results of the NSABP B32 trial, in conjunction with the remaining studies support the use of SLNB for early stage breast cancer, though AD should still be strongly considered in patients with positive sentinel nodes. The ACOSOG Z0011 trial suggests that AD may be optional for patients with one or two positive sentinel nodes. However, the trial recruitment was stopped early and it is the only trial with data on this topic.

The ten randomized trials and the meta-analyses unequivocally demonstrate fewer post-surgical morbidities with SLNB. There are short term quality of life benefits from an easier recovery from surgery and long-term benefits in terms of lymphedema, neuropathy and range of motion of the arm.

Thus, there is solid evidence with reasonably long-term follow-up demonstrating that patients treated with SLNB have similar breast cancer outcomes as those treated with AD and unequivocal evidence that the morbidity is less with SLNB.

**TA Criterion 3 is met**

**TA Criterion 4:** The technology must be as beneficial as any established alternatives.

The accepted alternative to SLNB is AD. All of the trials described under TA Criterion 3 compared SLNB to AD. The trials demonstrated equivalent OS, DFS, and locoregional relapse rates through a median of eight years of follow-up in the largest
trial. In addition, SLNB causes less harm than AD.

**TA Criterion 4 is met**

**TA Criterion 5:** The improvement must be attainable outside of the investigational setting.

Several of the randomized clinical trials trained physicians to perform SLNB at more than one hundred sites. In early breast cancer, sentinel lymph node biopsy is more commonly performed than axillary dissection in the United States and is widely used around the world. Thus, there is ample real world evidence that SLNB is a procedure that can be learned by many surgeons. However, it is not a straightforward surgery. There have been a number of studies evaluating the learning curve for performing sentinel lymph node biopsy. Most agree that a training manual with detailed descriptions of the technique, intra-operative proctoring by a surgeon experienced in the technique, and between 20 and 40 cases are needed for proficiency. The American Society of Breast Surgeons guidelines should be used to credential surgeons prior to performing SLNB alone.

**TA Criterion 5 is met**
RECOMMENDATION

It is recommended that use of sentinel lymph node biopsy meets CTAF TA Criterion 1 through 5 for safety, effectiveness and improvement in net health outcomes for women with clinically node negative invasive breast cancer.

October 17, 2012

This is the first review of this technology by the California Technology Assessment Forum.
RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

No assessments on this technology were found on the BCBSA TEC website.

Canadian Agency for Drugs and Technologies in Health (CADTH)

No reports on this technology were found on the CADTH website.

National Institute for Health and Clinical Excellence (NICE)

NICE published its guideline on breast cancer in February 2009: NICE Clinical Guideline 80 - Early and locally advanced breast cancer: - diagnosis and treatment. The guideline states that “Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. Sentinel lymph node biopsy (SLNB) is the preferred technique….SLNB should be performed by a team that is validated in the use of the technique."

National Comprehensive Cancer Network (NCCN)

NCCN has an extensive guideline for physicians (The NCCN Guideline 3.2012: Invasive Breast Cancer) and a version written for patients (The NCCN Guideline for Patients 2.2011: Breast Cancer). These guidelines offer extensive and detailed information on the recommended use of SLNB and treatment recommendations based on the patient’s clinical history of breast cancer, current clinical status, and SLNB findings. The guideline emphasizes that SLNB should be performed by a team with documented experience in SLNB and the team should include the surgeons, radiation oncologists, nuclear medicine physicians, pathologists and medical oncologists. The physician guidelines can be found at

**Centers for Medicare and Medicaid Services (CMS)**

There is no National Coverage Determination code (NCD) for SNLB for breast cancer. Coverage is based on Local Coverage Determination (LCD).

**Agency for Healthcare Research and Quality (AHRQ)**

No reports on this technology were found at the AHRQ website.

**American College of Surgeons (ACS)**

ACS was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.

**American Society of Breast Surgeons (ASBS)**

ASBC was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.

**Association of Northern CA Oncologists (ANCO)**

ANCO was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.

**Society of Nuclear Medicine and Molecular Imaging (SNMMI)**

SNMMI was invited to provide an opinion and to send a representative to the CTAF public meeting.
Society of Surgical Oncology (SSO)

SSO was invited to provide an opinion on this technology and to send a representative to the CTAF public meeting.
ABBREVIATIONS

CTAF: California Technology Assessment Forum
AJCC: American Joint Committee on Cancer
TNM: Tumor, Node, Metastasis staging system
NSABP: National Surgical Adjuvant Breast and Bowel Project Protocol
cm: Centimeters
AD: Axillary Lymph Node Dissection
EBCTCG: Early Breast Cancer Trialist's Collaborative Group
ASCO: American Society of Clinical Oncology
DARE: Database of Abstracts of Reviews of Effects
FDA: US Food and Drug Administration
OS: Overall Survival
DFS: Disease-Free Survival
ALMANAC: Axillary Lymphatic Mapping Against Nodal Axillary Clearance
KiSS: This is a metastasis suppressor gene.
RCT: Randomized Controlled Trial
NS: Not significant
CI: Confidence Interval
NR: Not reported
HR: Hazard ratio
OR: Odds ratio
US: United States
IHC: Immunohistochemistry
IBC: Inflammatory Breast Cancer
GIVOM: Gruppo Interdisciplinare Veneto di Oncologia Mammaria
H&E: Hematoxylin and Eosin
ACOSOG: The American College of Surgeons Oncology Group (ACOSOG)
SNAC: Sentinel Node versus Axillary Clearance
UK: United Kingdom
US: United States
NZ: New Zealand
A: Technitium-99 labeled albumin colloid
Ant: Technitium-99 labeled antimony colloid
S: Technitium-99 labeled sulfur colloid
RI: Radioisotope at discretion of individual sites
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