1. **What did ACRIN 6666 evaluate?**
   a. This trial assessed the effects of adding annual screening breast ultrasound performed by expert trained physicians to annual screening mammography. Three rounds of screening were performed, and detailed outcomes were recorded.
   b. The trial also looked at the effects of performing one round of screening breast MRI, done in a subset of women after the three negative screening mammography and ultrasound exams.

2. **Who was in this study?**
   a. Approximately 2700 women with dense breast tissue and increased risk for breast cancer participated. More than half had a history of breast cancer (54%); others had a high risk profile using the Gail model (24%) or a lifetime risk >25% (19%).
   b. 612 of these women went on to have a screening MRI in addition to the screening regime described above.

3. **What did this trial not evaluate?**
   a. Because there was no control group, the effects of additional screening modalities on patient survival or mortality from breast cancer could not be assessed.
   b. Because the women recruited were above average risk, the effect of adding screening breast ultrasound and MRI on women of average risk cannot be assessed, even if they have dense breasts.
   c. The use of automated breast ultrasound was not assessed.

4. **What were the results of adding an annual screening ultrasound exam?**
   a. On average, the addition of screening ultrasound resulted in an additional 4.3 cancers per thousand women screened. In the second and third rounds of screening (incidence rounds), 3.7 additional cancers were found per thousand women who had already been screened by mammography.
   b. The addition of screening ultrasound increases the rates of follow up and biopsy recommendations while decreasing the positive predictive value of biopsy. Although recommendations for biopsy of lesions seen only by ultrasound were lower in the incidence rounds compared to the prevalence round, they were still substantial. Even in the incidence rounds, the addition of ultrasound resulted in biopsy of an additional 5% of women, over and above the 2% sent to biopsy based on mammography alone. Further, in the incidence rounds only 7.4% of lesions deemed suspicious only by ultrasound turned out to be malignant, much lower than the positive predictive value of mammography, which was 38% in the
incident screening rounds. Further, additional interventional procedures, cyst aspirations, also resulted from ultrasound screening.

c. For mammography alone, the number of screens needed to detect one cancer is 127. To detect one additional cancer after negative screening mammograms, 234 screening ultrasound exams need to be performed. To detect one additional cancer after negative screening mammograms and ultrasounds, 68 screening MRIs need to be performed.

<table>
<thead>
<tr>
<th></th>
<th>Recall rate</th>
<th>Ca detection rate: CA/1000</th>
<th>Biopsy rate: Bx/screens</th>
<th>Biopsies yielding cancer</th>
<th>Women asked to return for short-term followup (BI-RADS 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammo: Round 1</td>
<td>11.5%</td>
<td>7.5</td>
<td>2.4%</td>
<td>29.2%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Mammo+US: Round 1</td>
<td>26.6%</td>
<td>12.8</td>
<td>10.2%</td>
<td>11.4%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Mammo: Rounds 2+3</td>
<td>9.4%</td>
<td>8.1</td>
<td>2.0%</td>
<td>38.1%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Mammo+US: Rounds 2+3</td>
<td>16.8%</td>
<td>11.8</td>
<td>7.0%</td>
<td>16.2%</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

5. **What were the results of adding a single screening breast MRI?**
   
a. After three rounds of negative screening mammograms and ultrasounds, in women who had a screening MRI, 14.7 additional cancers were found per thousand women (about 1.5% of women). This yield is four times greater than adding ultrasound to mammography screening.

b. Over half (58%) of women offered the opportunity to have MRI accepted. Overall, patients who accepted were younger, and had higher risk than patients who refused.

6. **What are some of the factors involved in implementation of screening ultrasound?**
   
a. Screening ultrasound exams in this study were performed by expert physicians who were specially trained for this study, and who used hand held ultrasound probes. Other methods of performing screening ultrasound and use of other personnel to perform the examination were not tested and may lead to higher recall and biopsy rates.
7. What are the implications for clinical practice?
   a. Although the addition of ultrasound to mammography for higher risk women with dense breasts can detect additional cancers, far more cancers can be found with the addition of screening MRI than with mammography alone.
   b. Screening ultrasound and MRI do not obviate the need for screening mammography.
   c. There is no need for screening ultrasound if screening is done with both mammography and breast MRI.
   d. The benefits of potential additional cancer detection must be weighed against the considerable potential for additional recommendations for biopsy and short interval follow-up.
   e. Facilities will need to choose if they want to offer screening ultrasound, and should not be obligated to do so. If facilities choose to do so, women should be informed of the possible implications of false positives.
   f. Facilities that perform screening ultrasound should be prepared to perform recommended biopsies and follow-up. Women should be encouraged to stay with the facility in which they received the screening.