Comparative Effectiveness Review

Number 19

Comparative Effectiveness of Core-Needle and Open Surgical Biopsy for the Diagnosis of Breast Lesions

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strengths and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Background

Breast cancer is the second most common malignancy of women, with over 180,000 new cases diagnosed each year in the United States. Survival rates depend on the stage of disease at diagnosis. Women diagnosed with early stages of breast cancer have a 5-year survival rate near 100 percent. However, early breast cancer is asymptomatic, and the only way to detect it is by population-wide screening programs that include regular mammography and physical examination.

Mammography uses x-rays to examine the breast for calcifications, masses, or other abnormal structures. Currently, most professional organizations recommend that all women 50 years of age and over receive a mammogram every 1 to 2 years. Many professional organizations recommend that routine breast cancer screening begin earlier, at age 40, although x-ray mammography screening is less effective in younger women. Most experts believe that regular x-ray mammographic screening of all women ages 50-70 can reduce mortality from breast cancer.

The American College of Radiology has created a standardized system for reporting the results of mammography, the Breast Imaging Reporting and Data System (BI-RADS®). There are seven categories of assessment and recommendation:

0 Need additional imaging evaluation and/or prior mammograms for comparison.

1 Negative.

2 Benign finding.

3 Probably benign finding. Initial short-interval followup suggested.

4 Suspicious abnormality. Biopsy should be considered.

5 Highly suggestive of malignancy. Appropriate action should be taken.

6 Known biopsy-proven malignancy. Appropriate action should be taken.

After identification of an abnormality on screening mammography or physical examination, women typically undergo additional imaging studies (diagnostic mammography, ultrasound, magnetic resonance imaging [MRI]) and a physical examination. If these studies suggest the abnormality may be malignant, a biopsy of the suspicious area may be recommended. Biopsy material may be obtained by fine-needle aspiration, core-needle biopsy, or open surgical procedures.

Open surgical biopsy involves removing a sample of tissue from the suspicious area through a surgical incision. To aid in location of a nonpalpable lesion, it may be marked with a wire, dye, or carbon particles using an imaging method (mammography, ultrasound, MRI) to guide placement of the marker. The procedure may be performed under general anesthesia, sedation plus local anesthesia, or local anesthesia only. The surgeon may attempt to remove the entire lesion during the biopsy procedure (excisional biopsy) if the lesion is fairly small. After the tissue sample is removed, the incision is closed with sutures.

Open surgical biopsy is the “gold standard” or “reference standard” method of evaluating a suspicious breast lesion because it is thought to be very accurate in diagnosing these lesions. While generally considered safe, it is a surgical procedure that, like all surgeries, places the patient at risk of experiencing morbidities and, in rare cases, mortality. However, only 20 to 30 percent of women who undergo breast biopsy procedures are diagnosed with cancer. Exposing large numbers of women who do not have cancer to invasive surgical procedures may be considered an undesirable medical practice. A less invasive method for evaluation of suspicious breast lesions would be preferable if it were sufficiently accurate.

A core-needle biopsy is a procedure that involves removing small samples of breast tissue through a hollow core needle inserted through the skin. Basic core-needle biopsy uses a special 11-, 14-, or 16-gauge needle (the smaller the gauge, the larger the diameter of the needle). The suspicious lesion may be located by palpation or by imaging (stereotactic mammography, ultrasound, MRI). The procedure is usually performed under local anesthesia. Multiple core-needle samples may be taken from the suspicious area.

A variant on core-needle biopsy is vacuum-assisted biopsy. After locating the suspicious area by stereotactic mammography or ultrasound, the probe of the device is inserted into the suspicious area. The device uses vacuum suction to help remove tissue samples. Multiple samples may be taken from the suspicious area without reinserting the needle.

The primary goal of initial biopsy of any abnormality is to diagnose the abnormality as benign or malignant. Generally, only malignant lesions require invasive followup procedures such as surgical excision or lymph node evaluation. As discussed above, the majority of women who are sent for breast biopsy do not have malignant lesions and do not require followup surgery. Thus an accurate initial core-needle biopsy would in most cases allow women to avoid any open surgical procedure. If the core-needle biopsy suggests the lesion is malignant, lymph node exploration and lesion excision to clear margins could be performed during the follow-on surgical procedure. Women who are diagnosed with malignant lesions by open surgical biopsy are often subject to an additional surgical procedure to ensure the lesion has been completely removed and, in some cases, for lymph node evaluation. Therefore, an accurate method of performing core-needle biopsies may enable many women to avoid surgery altogether and reduce the number of surgical procedures women with malignancies must undergo.

Medical indications—such as size and location of the lesion, imaging characteristics of the lesion, and likelihood of eventual surgical excision—may direct the preference of one type of breast biopsy procedure over another. However, other factors—such as patient preferences, access, and practice and referral patterns—also influence decisions about which procedure should be performed.

The large number of possible methods of performing breast biopsy can be bewildering to patients and health care providers alike. Which method should one choose? Is a particular method clearly superior, or does the method of choice depend upon individual patient characteristics? We have performed a systematic review intended to evaluate the accuracy of different methods of performing breast biopsy and to explore what factor(s) may impact the accuracy and possible harms of different methods of performing breast biopsy.

Methods

The topic of this systematic review was nominated in a public process. The Key Questions were developed by a technical expert panel assembled by the Scientific Resource Center for the Agency for Healthcare Research and Quality (AHRQ). The medical literature was systematically searched for articles from December 1990 through September 11, 2009, that addressed the Key Questions.

Medical personnel usually want to see the results of at least one randomized controlled trial demonstrating that a medical procedure is safe, effective, and beneficial to patients before adopting the procedure into general clinical practice. However, it is generally acknowledged that early diagnosis and treatment of breast tumors leads to improved survival rates and quality of life. Women found to have benign lesions on biopsy are able to avoid unnecessary treatment and receive reassurance that they do not have breast cancer. Given the currently available alternatives, there is no need to conduct randomized controlled trials of breast biopsy procedures. Establishing that a type of breast biopsy is safer than open surgical biopsy while being as accurate or almost as accurate as open surgical biopsy is sufficient to justify its routine use.

Studies of diagnostic test performance compare the results of the experimental test to a reference test. The reference test is intended to measure the "true" disease status of each patient. For the diagnosis of breast cancer, the "gold standard" reference test is open surgery and pathological examination of the removed tissue. However, a difficulty with the use of this reference standard in large cohort studies of screening-detected breast abnormalities is that many women with lesions that are probably benign will be subjected to open surgery. The principle of clinical equipoise means that there is genuine uncertainty over whether or not the intervention will be beneficial, and therefore it is acceptable to study the intervention in a clinical research trial. Subjecting women with lesions that are probably benign to open surgery does not meet the principle of clinical equipoise. Therefore we have chosen to include studies that used a combination of followup and open surgical biopsy as the reference standard in our analyses.

Studies of diagnostic test performance were examined to see if they met the inclusion criteria. In brief, the inclusion criteria were: the study directly compared core-needle biopsy to pathological examination of tissue obtained by open surgery and/or patient followup for at least 6 months; the study enrolled 10 or more patients at average risk of primary breast cancer who were referred for breast biopsy after discovery of a possible breast abnormality on screening mammography, routine physical examination, or routine self-examination; the study was a full-length article published in English; and 50 percent or more of the enrolled subjects completed the study.

In our analysis of biopsy accuracy, we focused on measures that evaluate the extent of false-negative errors (cancers falsely diagnosed as benign): sensitivity and negative likelihood ratio. Sensitivity is expressed as a percentage. A biopsy method with a sensitivity close to 100 percent will miss very few cancers. A negative likelihood ratio can be used to calculate an individual woman's risk of having a malignancy following a "benign" diagnosis on breast biopsy. In general, the smaller the negative likelihood ratio, the more accurate the diagnostic test is in predicting the absence of disease. However, each individual woman's post-test risk varies by her individual pre-test risk of malignancy.

We also analyzed the "underestimation rate." Lesions diagnosed by core-needle biopsy as ductal carcinoma in situ (DCIS, a noninvasive early stage of breast cancer) that were found to be invasive by the reference standard were counted as DCIS underestimates. Similarly, lesions diagnosed by core-needle biopsy as benign atypical ductal hyperplasia (ADH) that were found instead to be invasive by the reference standard were counted as ADH underestimates. The underestimation rate was then calculated as the number of underestimates per number of DCIS (or ADH) diagnoses. In the primary analysis of sensitivity and negative likelihood ratio, underestimates were not considered to be missed cancers because current clinical practice is to suggest surgical removal of ADH and DCIS lesions, and thus underestimates would not have been "missed."

The quality of the included studies was evaluated using an internal validity rating instrument for diagnostic studies. The studies were rated as low, moderate, or high in quality for the assessment of accuracy outcomes. Data from the included articles were abstracted and analyzed. Where possible, the data were combined using a bivariate mixed-effects binomial regression meta-analysis model. Underestimation rates were combined using a random-effects meta-analysis. The summary likelihood ratios and Bayes theorem were used to compute post-test probabilities of a malignancy.

The strength of evidence supporting each major conclusion was graded as high, moderate, low, or insufficient. The grade was developed after consideration of the quality of the evidence base, the size of the evidence base, the consistency of the findings, and the robustness of the findings to sensitivity analyses.

Conclusions

Key Question 1. In women with a palpable or nonpalpable breast abnormality, what is the accuracy of different types of core-needle breast biopsy compared with open biopsy for diagnosis?

Our literature searches identified 107 studies of 57,088 breast lesions that met the inclusion criteria. All of the studies were diagnostic cohort studies that enrolled a population of women found to have suspicious breast abnormalities on routine screening (mammography and/or physical examination). The women were sent for various types of breast biopsies, and the accuracy of the breast biopsy was determined by comparing the results of the breast biopsy to the results of a combination of open surgery and patient followup. We graded the supporting evidence for these conclusions as low based on the low quality of the evidence base (i.e., greater potential for bias), although we rated the quantity, consistency, and robustness of the evidence base as sufficient. Our conclusions for Key Question 1 are summarized in Table Table A and Figures Figure A through D. Our key conclusions are stated below.

- Stereotactically guided vacuum-assisted core-needle biopsies have a sensitivity of 99.2 percent (95-percent confidence interval [CI]: 97.9 to 99.7 percent). Strength of evidence: Low.
- Stereotactically guided automated gun core-needle biopsies have a sensitivity of 97.8 percent (95-percent CI: 95.8 to 98.9 percent). Strength of evidence: Low.
- Ultrasound-guided vacuum-assisted core-needle biopsies have a sensitivity of 96.5 percent (95-percent CI: 81.2 to 99.4 percent). Strength of evidence: Low.

- Ultrasound-guided automated gun core-needle biopsies have a sensitivity of 97.7 percent (95-percent CI: 97.2 to 98.2 percent). Strength of evidence: Low.
- Freehand automated gun core-needle biopsies have a sensitivity of 85.8 percent (95-percent CI: 75.8 to 92.1 percent). Strength of evidence: Low.

There was insufficient evidence to estimate the accuracy of MRI-guided core-needle biopsies.

The included studies assumed that open surgical biopsy was 100-percent accurate. We obtained information about the actual accuracy of open surgical biopsy from a review article, and therefore a formal conclusion and strength of evidence rating was not derived for estimates about the accuracy of open surgical biopsy.

Key Question 2. In women with a palpable or nonpalpable breast abnormality, what are the harms associated with different types of core-needle breast biopsy compared with open biopsy for diagnosis?

We recorded the complications and harms reported by the 107 studies that met the inclusion criteria for Key Question 1. Our results are summarized in Table B. Severe complications following core-needle biopsy of any type are very rare, affecting fewer than 1 percent of procedures. Vacuum-assisted procedures may be associated with slightly more severe bleeding events than automated gun core-needle biopsies. The strength of evidence supporting the quantitative estimates of the frequency of complications is low. Information about harms of open surgical biopsy was scanty in the included studies, and we supplemented it with information from recent review articles. Therefore, the strength of the evidence was not rated for conclusions about the safety of open surgical biopsy. However, it is clear that core-needle biopsies have a lower risk of complications than do open surgical procedures.

In Figure E we present a simplified model of what might happen if the same cohort of 1,000 women underwent various types of breast biopsy. The theoretical cohort of women includes 300 women with malignant tumors and 700 women with benign lesions. The model is based on the point estimates of accuracy from our analyses and do not incorporate estimates of uncertainty of the point estimates. Refer to Figure A through D for a visual representation of the degree of uncertainty in the point estimates. The model assumes that all women with nonbenign diagnoses on their first biopsy procedure, including all women who had open surgical biopsy as their first biopsy procedure, will be subject to an open surgical excisional procedure.

We also performed a number of meta-regressions exploring the impact of various factors on the accuracy and harms of core-needle biopsies. Our findings from these meta-regressions are summarized in Table C. Use of image guidance and vacuum assistance improved the accuracy of core-needle biopsy; however, vacuum assistance increased the percentage of procedures complicated by severe bleeding and hematoma formation. Performing biopsies with patients seated upright increased the incidence of vasovagal reactions.

Our meta-regressions did not identify a statistically significant effect of the following factors on the results: needle size, method of verification of biopsy (open surgery, open surgery and at least 6 months' followup, or open surgery and at least 2

years' followup), whether the studies were conducted at a single center or at multiple centers, whether the studies were conducted in general hospitals or dedicated cancer clinics, or the country in which the study was conducted. The studies reported insufficient information about lesion characteristics, patient characteristics, or the training or experience of the persons performing the biopsies to explore the effect of such factors on the accuracy or harms of the biopsies.

Key Question 3. How do open biopsy and various core-needle techniques differ in terms of patient preference, availability, costs, availability of qualified pathologist interpretations, and other factors that may influence choice of a particular technique?

Due to the nature of Key Question 3, we did not use formal inclusion criteria, nor did we come to many formal evidence-based conclusions. We collected information relevant to the topic from many sources, including interviews with experts. There was general agreement that core-needle biopsy costs less than open surgical biopsy, consumes fewer resources, and is preferred by patients. Women were generally satisfied with the cosmetic results of core-needle procedures. Women who underwent a core-needle biopsy as their first invasive test to diagnose a breast cancer had, on average, fewer surgical procedures than women who underwent an open biopsy procedure as their first invasive test. One particularly important finding was that women diagnosed with breast cancer by core-needle biopsy were usually able to have their cancer treated with a single surgical procedure, but women diagnosed with breast cancer by open surgical biopsy often required more than one surgical procedure to treat their cancer (odds ratio 13.7, 95-percent CI: 5.6 to 34.6). Due to the consistency, robustness, and extremely large strength of association between the type of biopsy and the requirement for more than one surgery for treatment, we rated the strength of evidence supporting this conclusion as moderate. There was insufficient information available to evaluate the impact of equipment or pathologist availability.

Discussion

When making decisions about what type of biopsy to use, individual women and their health care providers will need to weigh the pros and cons of each type of biopsy for each individual woman. Open surgical biopsies are highly accurate; however, core-needle biopsies are associated with a much lower incidence of harms and morbidity. In addition, women who are diagnosed with cancer by core-needle biopsy undergo fewer surgeries during treatment than do women who are diagnosed with cancer by open biopsy. The crux of the decision then becomes the question, "Is core-needle biopsy accurate enough?" The answer to this question may vary depending on the individual woman's estimated prebiopsy chance of having cancer (an estimate derived from mammography results and other prebiopsy examination information) and an individual woman's desire to avoid risk. For some women, core-needle biopsy will never be accurate enough to satisfy their desire to know, for sure, whether they do or do not have cancer. For others, the greater safety and less invasive nature of core-needle biopsy are worth a small sacrifice in accuracy. During decisionmaking, women and health care providers also need to consider the clinical implications of a cancer missed on core-needle biopsy. In many cases, the cancer

will be detected on subsequent mammography. Women with negative core-needle biopsies should have careful diagnostic followup with clinical correlation as appropriate for the individual patient.

The ratings of low strength of evidence apply to the individual estimates of accuracy for each type of core-needle biopsy. Due to the poor reporting and low internal validity of the included studies, we are concerned that the studies may be consistently biased toward finding that core-needle biopsies are more accurate than they actually are. We have performed sensitivity analyses (Table D) of the impact of this possibility on our conclusions. For each biopsy method, we have estimated the post-test probability of a woman actually having cancer after a negative core-needle biopsy result (assuming the woman had a prebiopsy probability of having cancer of 30 percent). We calculated probabilities using the summary estimate of the negative likelihood ratio from our analysis, and for summary estimates calculated after assuming our analysis had overestimated the sensitivity of the procedure by 1 percent, 5 percent, and 10 percent. We are moderately confident that our analysis has not overestimated the sensitivity by as much as 10 percent, but we present the results of this sensitivity analysis as a "worst case" scenario. For example, for ultrasound (US) guidance vacuum-assisted core-needle biopsy, we estimated the probability of a woman actually having cancer after a negative core-needle biopsy result to be 2 percent. Sensitivity analyses using overestimation of the sensitivity by 5 percent and 10 percent suggest that this probability would increase to 3 percent and 6 percent, respectively.

Remaining Issues

Our systematic review has found that both stereotactically guided vacuum-assisted and US-guided core-needle biopsies are safer than open surgical biopsy and are almost as accurate as open surgical biopsy, justifying their routine use. However, well-reported retrospective chart reviews, retrospective database analyses, or prospective diagnostic accuracy studies are needed to address the as-yet-unanswered questions as to what factors affect the accuracy and harms of core-needle breast biopsy. Answers to such questions are important for both patients and clinicians when faced with the decision of what type of breast biopsy is best for each individual patient. In addition, our conclusions are rated as being supported by a low strength of evidence. The low rating is almost entirely due to the fact that the evidence base, while large, consists of universally poorly reported studies. The studies omitted important details about patients, methods, and sometimes results. The studies presented results in an often confusing and haphazard manner. The poor reporting made it difficult to determine whether or not the studies were likely to be affected by bias, and therefore we rated the evidence base as being of low quality. Publication of better reported diagnostic accuracy studies would permit verification that our conclusions are accurate and not influenced by biases in the studies included in this assessment. Additional studies of MRI-guided biopsy are necessary in order to evaluate the accuracy and safety of MRI guidance.

Summary

An overall summary of the findings and level of evidence for each biopsy type is presented in Table E. Based on currently available evidence, it appears reasonable to consider choosing certain core-needle biopsy procedures given the comparable sensitivity

and lower complication rates for some of the percutaneous methods. Our analyses found the highest sensitivity for methods utilizing stereotactic guidance, particularly in conjunction with vacuum assistance. The appearance of breast lesions on imaging and the location within the breast may affect the type of core needle/imaging combination chosen for any particular woman. In general, women undergoing core needle biopsy are subjected to fewer surgical procedures overall than women who initially are diagnosed by open surgical biopsy, and they express satisfaction with the cosmetic results. However, the available studies suffered from poor reporting of important details that would help to identify patient and lesion characteristics that might impact the validity of this conclusion for individual women. We rated the strength of evidence as low for the accuracy outcomes, in large part because the absence of these details also compromised our ability to assess the risk of bias in the published studies. We have identified a number of questions that should be answered by future studies in order to improve individualized decisionmaking.

Table A. Summary of key accuracy findings (key Key question Question 1)

Type of biopsy	Number of missed cancers expected for every 1,000 biopsies[1]	Risk of malignancy following a "benign" test result[2]	Number of malignancies expected per 1,000 biopsy diagnoses of "high risk" lesion[3]	Number of invasive cancers expected per 1,000 biopsy diagnoses of DCIS	Strength of evidence supporting the conclusion
Open surgical[4]	3 to 6	0 to 1%	0	0	Not rated
Freehand automated gun	24 to 73	3.4 to 10%	Insufficient data to estimate		Low
US guidance automated gun	6 to 9	1 to 2%	234 to 359	271 to 450	Low
Stereotactic guidance automated gun	3 to 13	0.5 to 2%	357 to 517	180 to 321	Low
MRI guidance automated gun	Insufficient data to estimate				Insufficient
US guidance vacuum-assisted	2 to 56	0.3 to 8%	Insufficient data to estimate		Low
Stereotactic guidance vacuum-assisted	1 to 6	0.1 to 1%	177 to 264	111 to 151	Low

[1] For a population of women with a prevalence of malignancy of 30%, assuming a 100% specificity (no false positives).
[2] For a woman with a BI-RADS® 4 score following mammography expected to have an approximate prebiopsy risk of malignancy of 30%. Note that an individual woman's risk may be different from these estimates, depending on her own individual characteristics.
[3] Primarily ADH lesions.
[4] Estimates based on other literature reviews.

Abbreviations: ADH=atypical ductal hyperplasia; DCIS=ductal carcinoma in situ; MRI-=magnetic resonance imaging; US=ultrasound.

Table B. Summary of key harms findings (key Key Qquestion 2)

Type of biopsy	Number of deaths expected for every 1,000 biopsies	Number of cases of severe bleeding[1] expected for every 1,000 biopsies	Number of cases of hematomas requiring treatment expected for every 1,000 biopsies	Number of infections expected for every 1,000 biopsies	Strength of evidence supporting the conclusion
Open surgical[2]	0	Insufficient data to estimate	20 to 100	38 to 63	Not rated
Automated gun core needle	0	6	1	1	Low
Vacuum-assisted core needle	0	9	1	1	Low

[1] Although not all studies provided a definition of severe bleeding, those that did included episodes of bleeding necessitating treatment, including hospitalization or surgery.
[2] Estimates based on other literature reviews.

Table C. Summary of impact of various factors on accuracy and harms

Category	Factor	Impact on accuracy	Impact on harms	Strength of evidence supporting the conclusion
Patient characteristics	Insufficient data for any patient characteristics			Insufficient
Lesion characteristics	Insufficient data for any lesion characteristics			Insufficient
Biopsy methods	Patient position	Insufficient data	Vasovagal reactions occur more often in patients seated upright	Low
	Needle gauge	Does not affect accuracy	Insufficient data	Low
	Insufficient data for any other factor related to biopsy methods			Insufficient
Clinician characteristics	Operator experience	Accuracy improves with experience	Insufficient data	Insufficient
	Insufficient data for any other factor related to clinician characteristics			Inconclusive
Facility type	Type of facility	Does not affect accuracy	Insufficient data	Low
	Geographic location of facility	Does not affect accuracy	Insufficient data	Low

Table D. Sensitivity analysis of impact of low quality evidence on the conclusions

	Post-biopsy probability of having cancer after a negative core-needle biopsy result[1]			
Type of biopsy	Analysis results	Analysis overestimated sensitivity by 1% (e.g., sensitivity 97% rather than 98%)	Analysis overestimated sensitivity by 5% (e.g., sensitivity 93% rather than 98%)	Analysis overestimated sensitivity by 10% (e.g., sensitivity 88% rather than 98%)
Freehand automated gun	6%	6%	8%	9%
Ultrasound guidance automated gun	1%	1%	3%	5%
Stereotactic guidance automated gun	1%	1%	3%	5%
Ultrasound guidance vacuum-assisted	2%	2%	3%	6%
Stereotactic guidance vacuum-assisted	0.4%	0.8%	3%	5%

[1] For a woman with a BI-RADS® 4 score following mammography expected to have an approximate prebiopsy risk of malignancy of 30%. Note that an individual woman's risk may be different from these estimates, depending on her own individual characteristics.

Table E. Summary of all findings on comparative effectiveness of core-needle biopsy methods

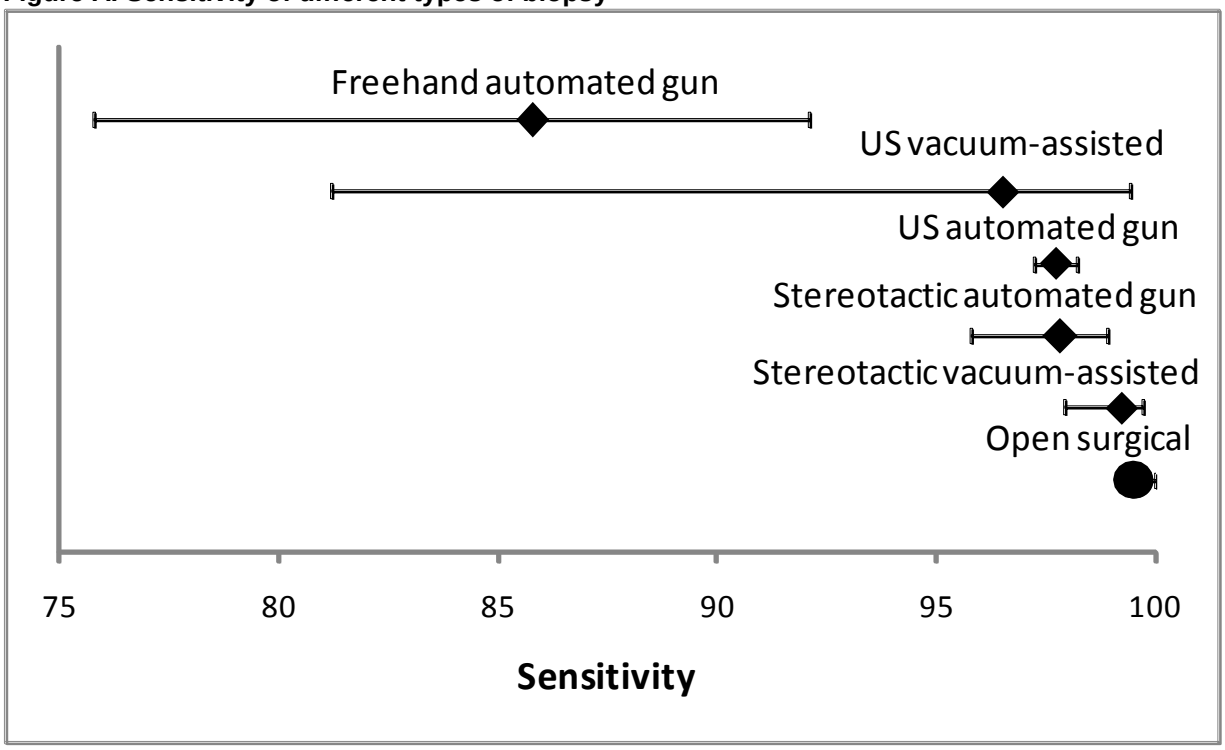
Accuracy			
Type of guidance	**Method of biopsy**	**Level of evidence**	**Sensitivity (95% CI)**
Any or none	Open surgical	Not rated	98 to 99%
Stereotactic	Automated gun	Low	97.8 (95.8 to 98.9)
	Vacuum-assisted	Low	99.2% (97.9 to 99.7)
Ultrasound	Automated gun	Low	97.7% (97.2 to 98.2)
	Vacuum-assisted	Low	96.5% (81.2 to 99.4)
MRI	Automated gun	Insufficient	83.3% (43.5 to 96.5)
Freehand	Automated gun	Low	85.8% (75.8 to 92.1)
Type of guidance	**Method of biopsy**	**Level of evidence**	**Negative likelihood ratio (95% CI)**
Any or none	Open surgical	Not rated	0.00 to 0.025
Stereotactic	Automated gun	Low	0.022 (0.012 to 0.043)
	Vacuum-assisted	Low	0.0090 (0.003 to 0.023)
Ultrasound	Automated gun	Low	0.030 (0.022 to 0.040)
	Vacuum-assisted	Low	0.036 (0.0060 to 0.21)
MRI	Any	Insufficient	0.23 (0.05 to 0.95)
Freehand	Automated gun	Low	0.14 (0.082 to 0.25)
Type of guidance	**Method of biopsy**	**Level of evidence**	**DCIS underestimation rate (95% CI)**
Any or none	Open surgical	Not rated	0.0%
Stereotactic	Automated gun	Low	24.4% (18.0 to 32.1)
	Vacuum-assisted	Low	13.0% (11.1 to 15.1)
Ultrasound	Automated gun	Low	35.5% (27.1 to 45.0)
	Vacuum-assisted	Insufficient	Not possible to calculate
MRI	Any	Insufficient	Not possible to calculate
Freehand	Automated gun	Insufficient	Not possible to calculate
Type of guidance	**Method of biopsy**	**Level of evidence**	**ADH underestimation rate (95% CI)**
Any or none	Open surgical	Not rated	0.0%
Stereotactic	Automated gun	Low	43.5% (35.7 to 51.7)
	Vacuum-assisted	Low	21.7% (17.7 to 26.4)
Ultrasound	Automated gun	Low	29.2% (23.4 to 35.9)
	Vacuum-assisted	Insufficient	Not possible to calculate
MRI	Any	Insufficient	Not possible to calculate
Freehand	Automated gun	Insufficient	Not possible to calculate
Factors potentially affecting accuracy			
Factor category	**Factor**	**Level of evidence**	**Conclusion about impact of factor on accuracy**
Patient characteristics	Patient age	Insufficient	No conclusion possible
	Breast density	Insufficient	No conclusion possible
	Patient comorbidities	Insufficient	No conclusion possible
Lesion characteristics	Palpable vs. nonpalpable	Insufficient	No conclusion possible
	Microcalcifications vs. masses	Insufficient	No conclusion possible
	Distortions vs. masses	Insufficient	No conclusion possible
	Size of lesion	Insufficient	No conclusion possible
	Location of lesion	Insufficient	No conclusion possible
Biopsy methodology	Number of cores	Insufficient	No conclusion possible
	Patient position	Insufficient	No conclusion possible
	Reference standard	Not rated	The type of reference standard (open surgery, 2 years of followup, or only 6 months of followup) had no impact on the data reported by the studies about the accuracy of core-needle biopsy

Factors potentially affecting accuracy (continued)			
Factor category	**Factor**	**Level of evidence**	**Conclusion about impact of factor on accuracy**
	Use of vacuum	Low	Vacuum assistance improved accuracy
	Use of image guidance	Low	Use of image guidance improved accuracy; stereotactic guidance was more accurate than US guidance
	Size of needle	Not rated	The size of the needle did not affect the accuracy of the procedure
Clinician and facility factors	Experience of operator	Insufficient	No conclusion possible
	Training of operator	Insufficient	No conclusion possible
	Facility location	Not rated	The location of the facility had no impact on the accuracy of core-needle biopsy
	Facility type	Not rated	The type of facility had no impact on the accuracy of core-needle biopsy
Harms			
Harm category	**Harm**	**Level of evidence**	**Conclusion**
Number of surgeries required	Undergoing surgery	Moderate	Women diagnosed with breast cancer by core-needle biopsies are more likely to be able to be treated with a single surgical procedure than women diagnosed with breast cancer by open surgical biopsies
Complications	Any	High	Core-needle biopsies have a lower risk of complications than open surgical procedures
Severe complications	Any	Low	2 to 10% of open surgical procedures may be affected by severe complications; 0.09 to 0.72% of core-needle biopsy procedures may be affected by severe complications
	Deaths	Low	No deaths were reported in association with any type of breast biopsy procedure
	Bleeding severe enough to require treatment	Low	0.72% of core-needle procedures were affected by severe bleeding
	Hematomas requiring treatment	Low	0.09% of core-needle procedures were affected by hematomas requiring treatment
	Infections	Low	0.15% of core-needle procedures were affected by infections requiring antibiotic treatment
	Severe pain	Low	1.7% of patients reported experiencing severe pain during core-needle procedures
Minor complications	Bruising	Low	Bruising following core-needle procedures was reported to be common
	Vasovagal reactions	Low	1.0% of patients had vasovagal reactions during core-needle procedures
	Pain	Low	3.7% of patients required pain medications following core-needle procedures
Factors potentially affecting harms			
Factor category	**Factor**	**Level of evidence**	**Conclusion about impact of factor on harms**
Patient characteristics	Patient age	Insufficient	No conclusion possible
	Breast density	Insufficient	No conclusion possible
	Patient comorbidities	Insufficient	No conclusion possible
Lesion characteristics	Palpable vs. nonpalpable	Insufficient	No conclusion possible
	Microcalcifications vs. masses	Insufficient	No conclusion possible
	Distortions vs. masses	Insufficient	No conclusion possible

Factors potentially affecting harms (continued)			
Factor category	**Factor**	**Level of evidence**	**Conclusion about impact of factor on harms**
	Size of lesion	Insufficient	No conclusion possible
	Location of lesion	Insufficient	No conclusion possible
Biopsy methodology	Number of cores	Insufficient	No conclusion possible
	Patient position	Low	Vasovagal reactions occur more often in patients seated upright
	Reference standard	Insufficient	No conclusion possible
	Use of vacuum	Low	Use of vacuum increased the percentage of procedures complicated by severe bleeding and hematoma formation
	Use of image guidance	Insufficient	No conclusion possible
	Size of needle	Insufficient	No conclusion possible
Clinician and facility factors	Experience of operator	Insufficient	No conclusion possible
	Training of operator	Insufficient	No conclusion possible
	Facility location	Insufficient	No conclusion possible
	Facility type	Insufficient	No conclusion possible

Abbreviations: ADH=atypical ductal hyperplasia; CI=confidence interval; DCIS=ductal carcinoma in situ; MRI=magnetic resonance imaging; US=ultrasound.

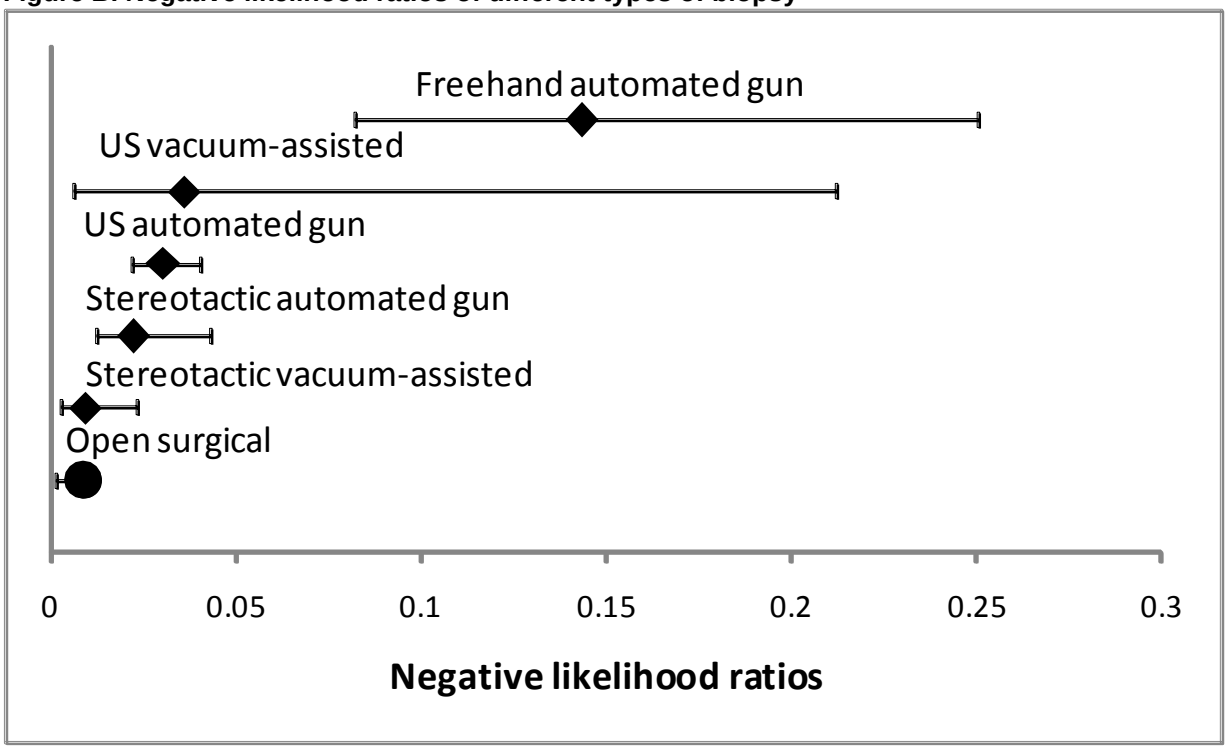
Figure A. Sensitivity of different types of biopsy



Sensitivity = (true positives/ (true positives + false negatives))*100.
Freehand automated gun: 5 studies of 610 biopsies.
US vacuum-assisted: 7 studies of 507 biopsies.
US automated gun: 16 studies of 7,124 biopsies.
Stereotactic automated gun: 33 studies of 7,135 biopsies.
Stereotactic vacuum-assisted: 22 studies of 7512 biopsies.
Open surgical estimate based on other literature reviews.

Abbreviation: US=ultrasound.

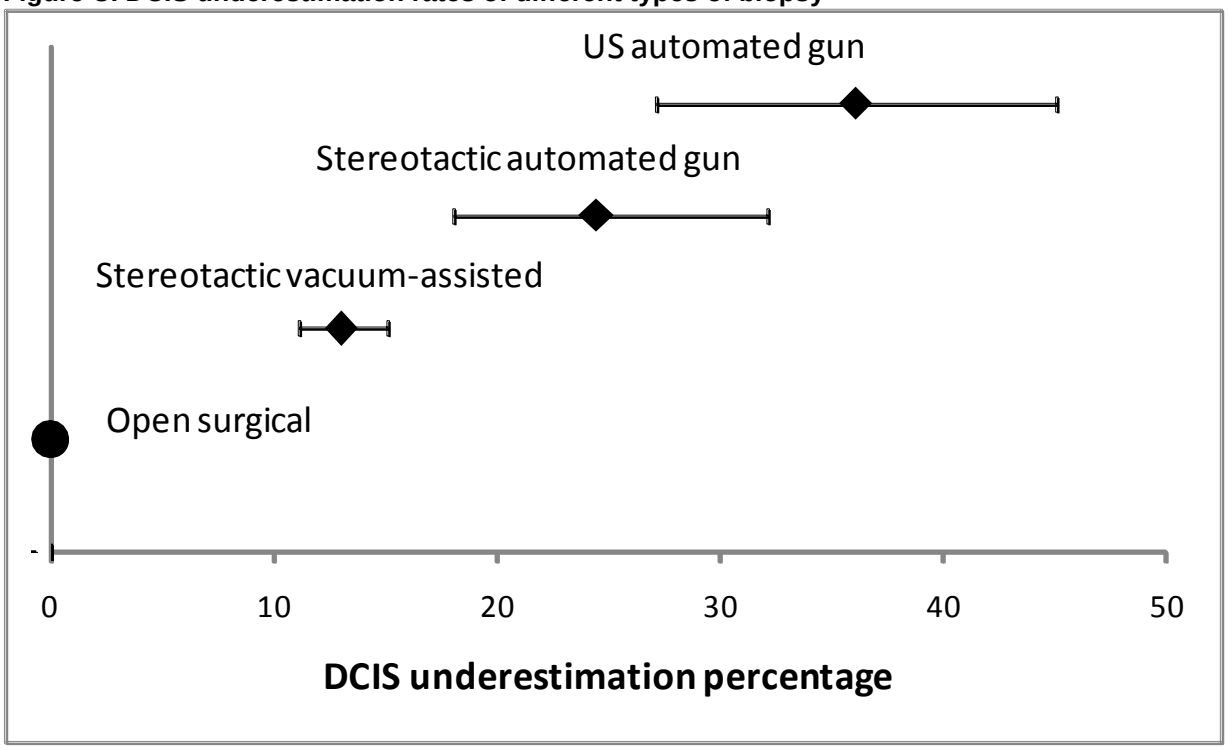
Figure B. Negative likelihood ratios of different types of biopsy



Negative likelihood ratio = (false negatives/(true positives + false negatives)/(true negatives/ false positives + true negatives).
Freehand automated gun: 5 studies of 610 biopsies.
US vacuum-assisted: 7 studies of 507 biopsies.
US automated gun: 16 studies of 7,124 biopsies.
Stereotactic automated gun: 33 studies of 7,135 biopsies.
Stereotactic vacuum-assisted: 22 studies of 7,512 biopsies.
Open surgical estimate based on other literature reviews.

Abbreviation: US=ultrasound.

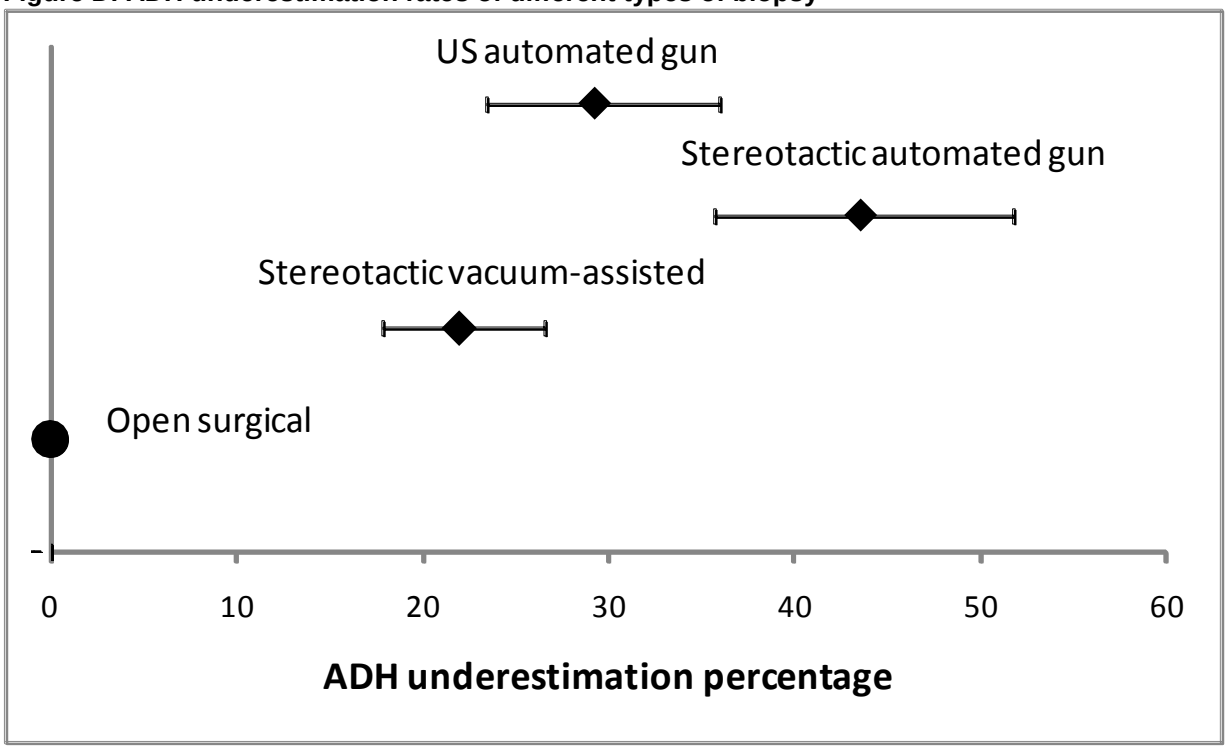
Figure C. DCIS underestimation rates of different types of biopsy



DCIS underestimation = (number cases diagnosed as DCIS on core-needle biopsy that were found to be invasive cancer by the reference standard)/ (total number cases diagnosed as DCIS on core-needle biopsy)*100.
US automated gun: 12 studies of 208 core-needle diagnoses of DCIS.
Stereotactic automated gun: 19 studies of 694 core-needle diagnoses of DCIS.
Stereotactic vacuum-assisted: 21 studies of 1,224 core-needle diagnoses of DCIS.
Open surgical estimate based on other literature reviews.

Abbreviations: DCIS=ductal carcinoma in situ; US=ultrasound.

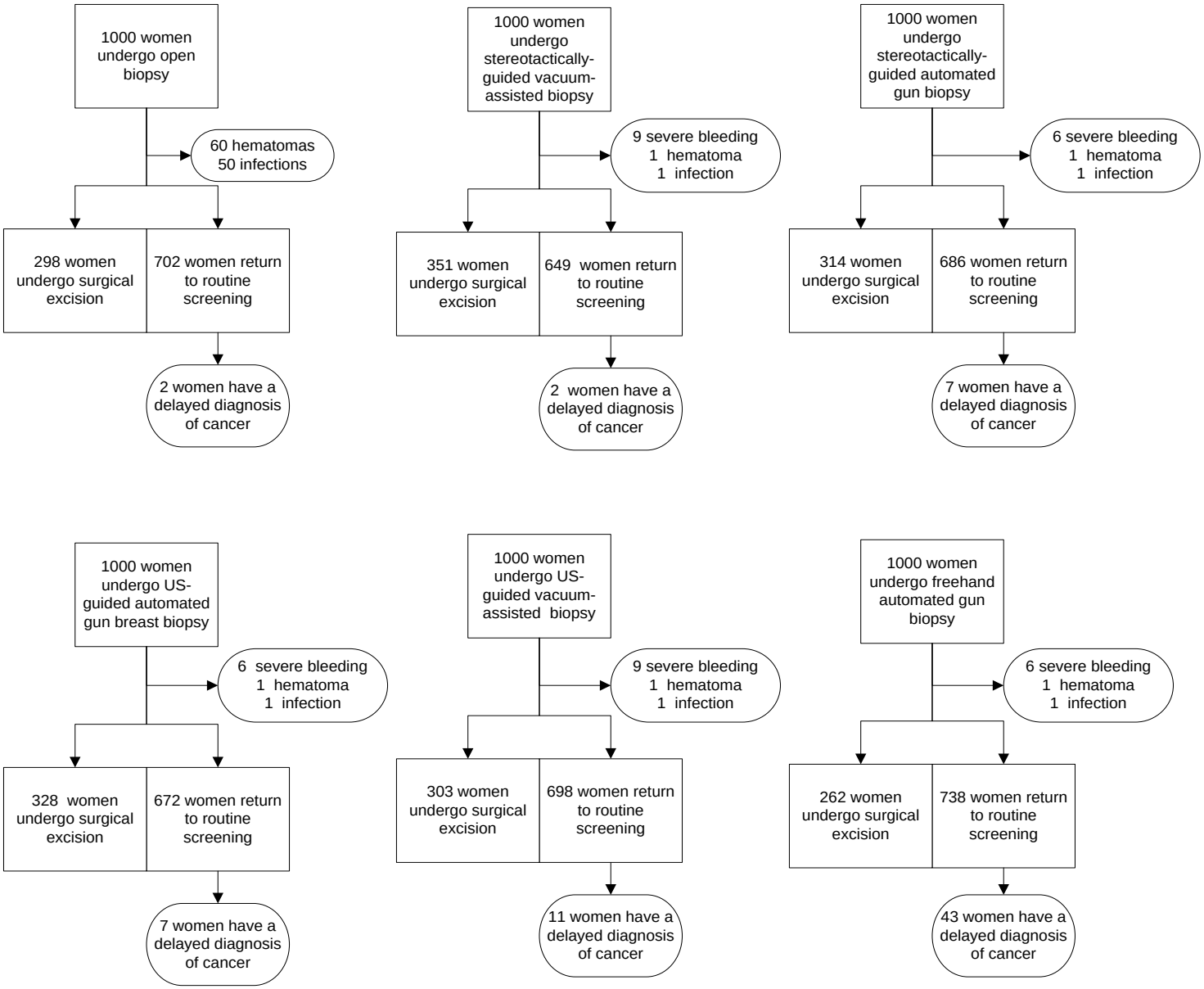
Figure D. ADH underestimation rates of different types of biopsy



ADH underestimation = (number cases diagnosed as ADH on core-needle biopsy that were found to be invasive or in situ cancer by the reference standard)/ (total number cases diagnosed as ADH on core-needle biopsy)*100.
US automated gun: 13 studies of 207 core-needle diagnoses of ADH.
Stereotactic automated gun: 26 studies of 321 core-needle diagnoses of ADH.
Stereotactic vacuum-assisted: 21 studies of 380 core-needle diagnoses of ADH.
Open surgical estimate based on other literature reviews.

Abbreviations: ADH-=atypical ductal hyperplasia; US=ultrasound.

Figure E. Models of 1,000 women undergoing breast biopsy



Abbreviation: US=ultrasound.

The numbers may not sum to exactly 1,000 due to rounding.

Chapter 1. Introduction

Background

Breast Cancer

Breast cancer is the second most common malignancy of women.[1] The American Cancer Society estimates that in the U.S. in 2009, 67,280 women will have been diagnosed with new cases of *in situ* cancer, 192,370 women will have been newly diagnosed as having invasive breast cancer, and there will be 40,170 deaths due to this disease.[2] In the general population, the cumulative risk of being diagnosed with breast cancer by age 70 is estimated to be 6% (lifetime risk of 13%).[3,4]

Ductal carcinoma, including ductal carcinoma *in situ* (DCIS), is the most common malignancy of the breast. It arises within the ducts of the breast. DCIS is early breast cancer confined to the inside of the ductal system, and invasive (also called infiltrating) ductal carcinoma is a later stage that has broken through the walls of the ducts and invaded nearby tissues. Lobular carcinoma is similar to ductal carcinoma, first arising in the terminal ducts of the lobules and then invading through the walls of the ducts and into nearby tissues. Atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) are caused by abnormal cellular proliferation within the terminal ducts of the lobules. The two conditions are distinguished primarily by the degree to which the ducts are filled by cells, and some pathologists have suggested the use of the term lobular neoplasia to describe a continuum of disease from ALH to LCIS.[5] LCIS is not usually detectable by routine clinical exam or mammograms; it is, however, occasionally detected as an incidental finding at the time a breast biopsy is performed for other reasons. Women diagnosed with ALH or LCIS are at elevated risk of developing an invasive carcinoma in the future.

Other types of benign breast abnormalities that have been linked to an elevated risk of invasive carcinoma or a finding of associated invasive carcinoma upon excision are atypical ductal hyperplasia (ADH), papillary lesions, and radial scars.[5]

Breast Biopsy

Breast cancer is usually first detected by feeling a lump on physical examination (either self-examination or an exam conducted by a health practitioner) or by observing an abnormality during x-ray screening mammography. Survival rates depend on the stage of disease at diagnosis. At stage 0 (carcinoma *in situ*) the five-year survival rate is close to 100%. The five-year survival rate for women with stage IV (cancer that has spread beyond the breast) is only 27%.[6] These observations suggest that breast cancer mortality rates can be significantly reduced by identifying cancers at earlier stages. Because early breast cancer is asymptomatic, the only way to detect it is through population-wide screening. Mammography is a widely accepted method for breast cancer screening.[7,8]

Mammography uses x-rays to examine the breast for clusters of microcalcifications, circumscribed and dense masses, masses with indistinct margins, architectural distortion compared with the contralateral breast, or other abnormal structures. Currently, most professional organizations recommend that all women older

than fifty years of age receive an annual or biennial mammogram.[6,9] Some professional organizations recommend that routine breast cancer screening begin earlier, at age 40, although x-ray mammography screening is less effective in younger women.[7] Most experts believe that regular x-ray mammographic screening of all women who are between the age of 50 and 70 can reduce mortality from breast cancer.[6-8] The United States Preventive Services Task Force (USPSTF) recommends screening mammography every 2 years for women aged 50 to 74.[10]

The American College of Radiology has created a standardized system for reporting the results of mammography, the Breast Imaging Reporting and Data System (BI-RADS®).[11-13] There are seven categories of assessment and recommendation:

0 Need additional imaging evaluation and/or prior mammograms for comparison

1 Negative

2 Benign finding

3 Probably benign finding. Initial short interval follow-up suggested

4 Suspicious abnormality. Biopsy should be considered.

5 Highly suggestive of malignancy. Appropriate action should be taken.

6 Known biopsy-proven malignancy. Appropriate action should be taken.

After identification of a possible abnormality on screening mammography or physical examination, women typically undergo additional imaging studies (e.g., diagnostic mammography, ultrasound, possibly magnetic resonance imaging (MRI)) and a physical examination. If these studies suggest the abnormality may be malignant, a biopsy of the suspicious area may be recommended. Biopsy material may be obtained by fine-needle aspiration, core-needle biopsy, or open surgical procedures. The combination of physical examination, imaging studies, and fine-needle aspiration is sometimes referred to as the "triple assessment."[14] Fine-needle aspiration is not the topic of this report and is not discussed further.

Open surgical biopsy involves removing a sample of tissue from the suspicious area through an open incision. To aid in location of a non-palpable lesion, it may be marked with a wire, dye, or carbon particles using an imaging method (e.g., mammography, ultrasound, MRI) to guide placement of the marker. The biopsy procedure may be performed under general anesthesia, sedation plus local anesthesia, or local anesthesia only. The surgeon may attempt to remove the entire lesion during the biopsy procedure (excisional biopsy) if the lesion is fairly small. After removing the tissue sample, the incision is closed with sutures.

Open surgical biopsy is the reference standard for evaluating a suspicious breast lesion because it is thought to be very accurate in diagnosing these lesions. However, it is a surgical procedure that, like all surgeries, places the patient at risk of experiencing morbidities and, in rare cases, mortality. Lacquement et al. examined a series of 668 women who underwent biopsy, and reported that only 23% of these women were diagnosed with breast cancer after biopsy.[15] Exposing large numbers of women who do not have cancer to invasive surgical procedures may be considered an undesirable medical practice. A less invasive method for evaluation of suspicious breast lesions would be preferable if it were sufficiently accurate.

A core-needle biopsy is a procedure that involves removing small samples of breast tissue through a hollow core needle inserted through the skin. Basic core-needle biopsy uses a special 11-, 14-, or 16-gauge needle (the smaller the gauge the larger the diameter of the needle). The suspicious lesion may be located by palpation or by imaging (e.g., stereotactic mammography, ultrasound, MRI). The procedure is usually performed under local anesthesia. Multiple core-needle samples may be taken from the suspicious area.

A variant on core-needle biopsy is vacuum-assisted biopsy. After locating the suspicious area by stereotactic mammography, ultrasound, or MRI, the probe of the device is inserted into the suspicious area. The device uses vacuum suction to help remove tissue samples. Multiple samples may be taken from the suspicious area. Some vacuum-assisted devices, unlike traditional core-needle biopsy devices, can collect multiple samples while only needing to be inserted through the skin once.

Another variant on core-needle biopsy is large core breast biopsy. Large core breast biopsy is intended to be a minimally invasive method of removing a fairly large sample of breast tissue, or even to remove an entire small lesion. After locating the suspicious area by stereotactic mammography a wire is inserted to mark the location. The device then removes a large core of breast tissue through a cannula. Sutures are required to close the skin at the entry site. There were no large core biopsy devices commercially available in the United States at the time this report was prepared.

Initial biopsy of any breast abnormality has a primary goal of making a diagnosis of the abnormality as benign or malignant. Generally, only malignant lesions require invasive follow-up procedures such as surgical excision or lymph node evaluation. As discussed above, the majority of women who are sent for breast biopsy do not have malignant lesions and do not require follow-up surgery. Thus an accurate initial core-needle biopsy would allow women with benign findings to avoid an open surgical procedure. If the core-needle biopsy suggests the lesion is malignant, lymph node exploration and lesion excision to clear margins could be performed during a subsequent open procedure. Women who are diagnosed with malignant lesions by open biopsy are often subjected to additional follow-up surgical procedures to ensure the lesion has been completely removed and, in some cases, for lymph node evaluation. Therefore, an accurate method of performing core-needle biopsies may enable many women to avoid surgery altogether and reduce the number of surgical procedures women with malignancies must undergo.

Prognostic and Predictive Factors

Pathological prognostic and predictive factors are used in clinical practice to guide treatment planning. One of the major concerns about core-needle biopsy techniques is under-sampling of important areas of the lesion. If important areas are missed, the pathology report may be misleading. Categories of prognostic and predictive factors include tumor type, histological grade, and immunophenotype of the tumor. These categories are briefly discussed below.

Tumor typing is evaluation of type of the tumor, e.g., DCIS, infiltrating ductal carcinoma, medullary carcinoma, infiltrating lobular carcinoma, tubular carcinoma, mucinous carcinoma, inflammatory breast cancer, or other. Tumor typing of mixed-type

tumors by core-needle biopsy may be incorrect due to the inability of needle biopsy to sample all parts of the tumor.

Histological grade is used to describe invasive tumors and other breast abnormalities. The grade is based on how closely cells in the sample tissue resemble normal breast tissue. Different grading systems are in use, but in general the higher the grade, the more abnormal the tissue structure and cells. Interpretation of grade from core-needle biopsy material has been reported to commonly underestimate the grade by one level as compared to surgical specimens.[16] Rakha and Ellis have suggested that the discrepancy is often due to the fact that core-needle samples are generally taken from the interior of the tumor and surgical specimens for grading are usually taken from the periphery of the tumor, where the most active growth is occuring.[16]

Immunophenotype of the tumor refers to determining the status of certain biomarkers. The presence of estrogen receptors, progesterone receptors, and HER-2 overexpression are important features of tumor biology that need to be incorporated into treatment decisions. For example, estrogen receptor positive tumors may be effectively treated with hormone-blocking medications such as tamoxifen, and tumors that over-express HER-2 may be treated with trastuzumab (Herceptin) or lapatinib (Tykerb). Core-needle specimens can be utilized in tests to determine the immunophenotype of the tumor.

Staging

Final treatment decisions are based on the stage of the tumor. Breast cancer is most commonly staged with the American Joint Committee on Cancer (AJCC) TNM system.[17] The “T” stands for tumor, and is assigned a number from 0 to 4 to describe the size and local spread of the primary tumor, determined by imaging studies such as mammography, MRI, and CT scanning. The ‘N” stands for lymph nodes, and is assigned a number from 0 to 3 to indicate whether the cancer has spread to the lymph nodes and to how many lymph nodes, determined by sentinel lymph node biopsy or axillary lymph node dissection. The “M” stands for distant metastasis, and is assigned either 0 or 1 to indicate whether the cancer has spread to distant locations, determined by imaging studies such as CT scanning and bone scintigraphy.[18] Breast cancer stage may also be expressed as a number from 0 to IV, where stage 0 is ductal carcinoma in situ (DCIS) and stage IV is metastatic cancer.[17,18]

Negative Surgical Excision after After Core-Needle Biopsy

Sometimes a core-needle biopsy specimen suggests that a tumor is present, and thus an open surgical procedure is performed, only to find no tumor present. Many experts suggest that in these cases the core-needle biopsy procedure removed the entire tumor.[16] This may be the case. It is also possible that the pathology report for either procedure was incorrect, or that the open procedure missed the lesion.

Choice of Biopsy Method

Medical indications may direct the preference for one type of procedure over another. For example, the size and location of the lesion, imaging characteristics of the lesion, and likelihood of eventual surgical excision could be important to the choice of

method. However, other factors such as patient preferences, access, and practice and referral patterns also influence decisions about which procedure should be performed.

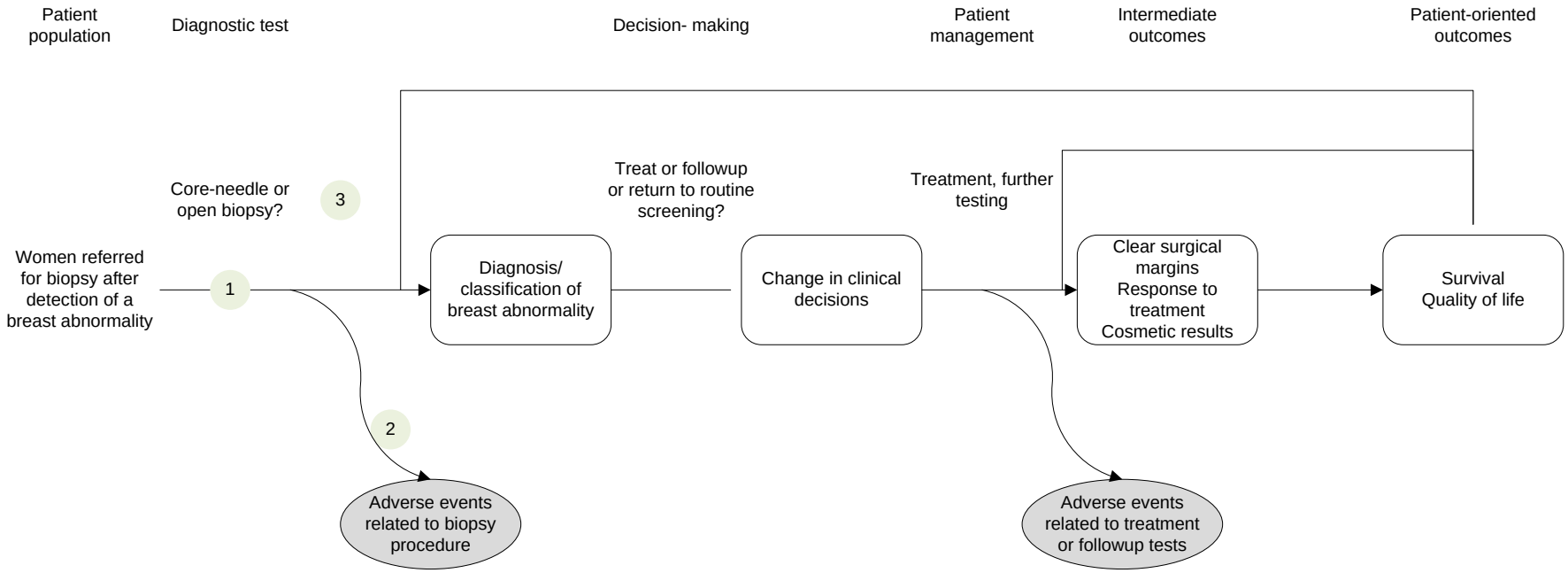
The large number of possible methods of performing breast biopsy can be bewildering to patients and healthcare providers alike. Which method should one choose? Is a particular method clearly superior, or does the method of choice depend upon individual patient or lesion characteristics? We have performed a systematic review intended to evaluate the accuracy of different methods of performing breast biopsy, and to explore what factor(s) may impact the accuracy and possible harms of different methods of performing breast biopsy.

Conceptual Framework

The analytical framework (Figure 1) demonstrates the links between patients, tests, interventions, and outcomes. The numbers on the diagram refer to the Key Questions (see next section) and their placement in Figure 1 exhibits the many links separating the Key Questions from the patient-oriented outcomes. Fryback and Thornbury have proposed a six-level model of assessing diagnostic efficacy.[19] Level 1 is analytic validity; level 2 is diagnostic accuracy; level 3 is diagnostic thinking; level 4 is impact on choice of treatment; level 5 is patient-important outcomes; and level 6 is societal impact. Demonstration of efficacy at each lower level is logically necessary, but not sufficient, to assure efficacy at higher levels. This systematic review is primarily concerned with Level 2, the diagnostic accuracy of various methods of performing breast biopsies.

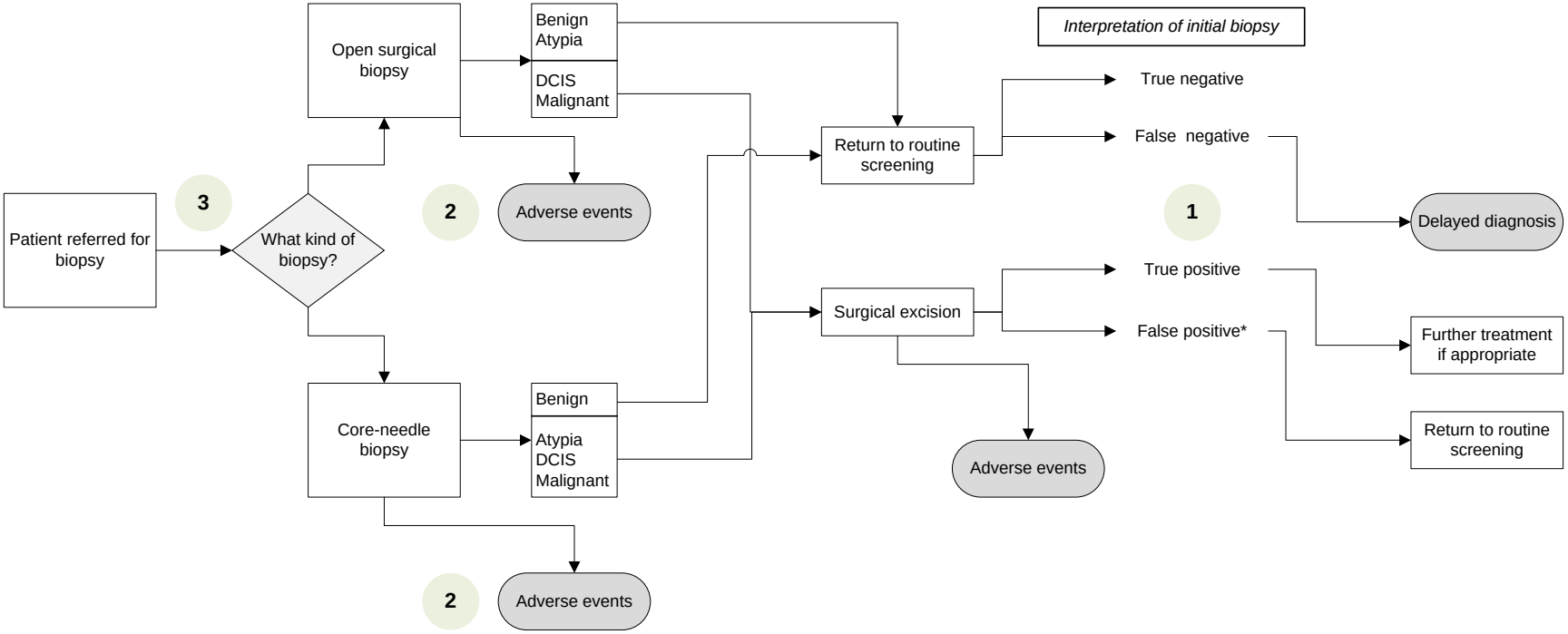
We have expanded the section of the analytical framework that is relevant to the questions addressed in this systematic review in a patient flow diagram (Figure 2). The numbers on the diagram refer to the Key Questions (see next section). We have simplified the diagram for clarity by combining all types of core-needle procedures together into one pathway.

Figure 1. Analytical framework



The numbers in the figure depict where the three Key Questions addressed in this report are located within the flow of the analytical framework.

Figure 2. Patient flow diagram



The numbers in the figure depict where the three Key Questions addressed in this report are located within the patient flow diagram.
*If initial core-needle biopsy indicates malignancy but surgical excision is negative for malignancy, many would assume that the initial biopsy removed the lesion rather than to label it a false positive. Patients may then undergo close surveillance or further treatment.

Diagnostic Test Characteristics

No diagnostic test is perfect. Studies of test performance compare test results on a group of individuals, some of whom have the disease and some of whom do not. Each individual undergoes the experimental test as well as a second reference test to determine "true" disease status. The relationship between the diagnostic test results and disease status is described using diagnostic test characteristics. It is important that the reference test is very accurate in measuring "true" disease status, or else the performance of the experimental diagnostic test will be poorly estimated.

Sensitivity and Specificity

The results of the experimental and reference standard test and their relationship are commonly presented as two-by-two (2x2) tables (see Table 1). From the 2x2 table, sensitivity and specificity are readily calculated:

Sensitivity = TP/(TP+FN)

Specificity = TN/(FP+TN)

Table 1. Example of a 2x2 table

		Disease	
		Present	**Absent**
Test Results	**Positive**	True positives (TP)	False positives (FP)
	Negative	False negatives (FN)	True negatives (TN)

Sensitivity and specificity are properties of a test that are useful when deciding whether to use a test. Sensitivity is the proportion of people with the disease who have a positive test for the disease. A test with high sensitivity will rarely misclassify people with the disease as not having the disease (the test has a low rate of false-negatives). Specificity is the proportion of people without the disease who have a negative test. A test with high specificity will rarely misclassify people without the disease as diseased (a low rate of false-positives).

Predictive Values and Likelihood Ratios

To make sense of a diagnostic investigation, a clinician needs to be able to make an inference regarding the probability that a patient has the disease in question according to the result obtained from the test. Sensitivity and specificity do not directly provide this information. The predictive values and likelihood ratios can also be directly calculated from a 2x2 table:

Positive predictive value = TP/(TP+FP)

Negative predictive value = TN/(FN+TN)

Positive likelihood ratio = (TP/(TP+FN))/(FP/(FP+TN))

Negative likelihood ratio = (FN/(TP+FN))/(TN/(FP+TN))

The positive predictive value of a test is the probability of a patient having the disease following a positive test result. The negative predictive value is the probability of a patient not having the disease following a negative test result. Predictive values describe the probabilities that positive or negative results are correct for an individual patient. However, predictive values depend on the prevalence of disease in the population. A study that enrolled a patient population with a disease prevalence of 70% may report a positive predictive value of 80%. If a clinician tests a patient from a population with a disease prevalence of 70%, and the test comes back

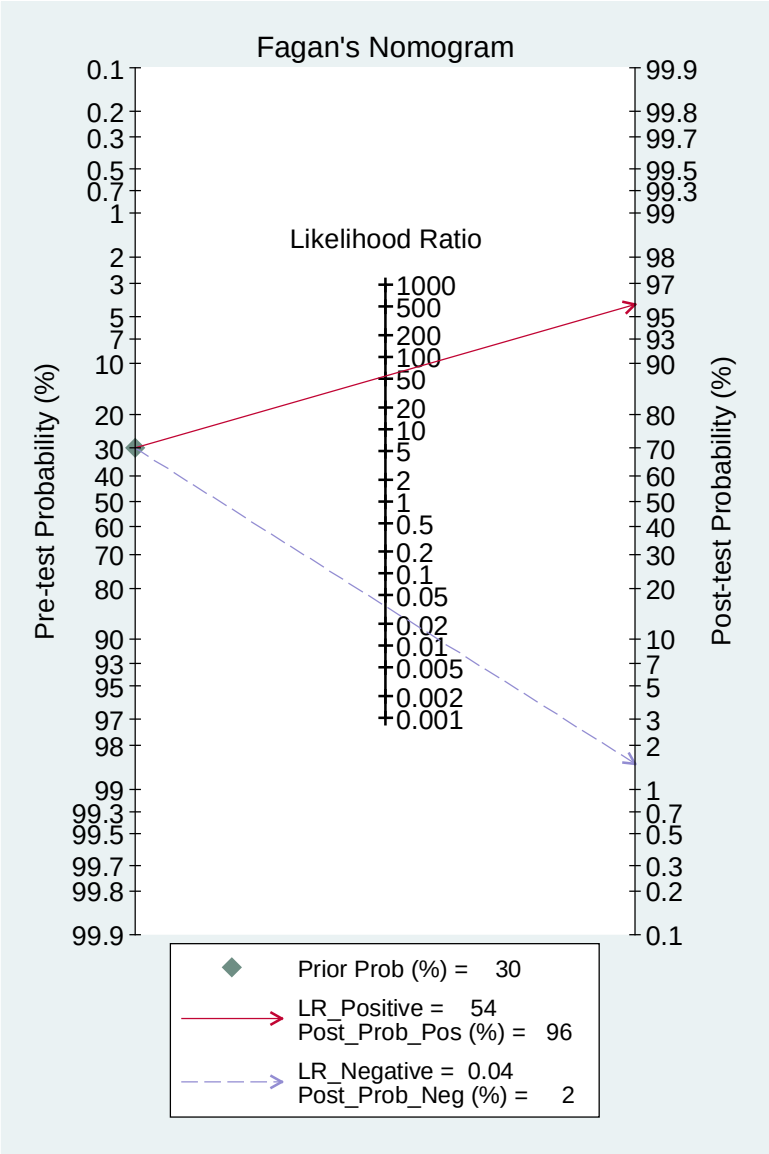
positive, the clinician knows the patient has an 80% chance of having the disease in question. However, if the patient comes from a population with a disease prevalence of 20%, the clinician cannot apply the results of the study directly to this patient.

Because sensitivity and specificity are difficult to directly apply to clinical situations, and predictive values vary markedly as a function of disease prevalence (i.e., may be different for each patient subpopulation) a combined measure of diagnostic performance, the likelihood ratio, is a clinically useful diagnostic test performance measure. Negative likelihood ratios measure the ability of the test to accurately "rule out" disease, and positive likelihood ratios measure the ability of the test to accurately detect disease.

Likelihood ratios are independent of prevalence and therefore can be directly applied in the clinic to update an individual's estimated chances of disease according to their test result. Likelihood ratios can be used in Bayes' theorem to calculate post-test odds of having a disease from the pre-test suspicion of the patient's odds of having that disease. Clinicians may be familiar with simple nomograms that allow a direct visualization of post-test chances of disease given a positive or negative test result, without the need to go through the tedious calculations of Bayes' theorem; see, for example, Figure 3 or the interactive form of the nomogram provided by the Center for Evidence-based Medicine at http://www.cebm.net.

In Figure 3 a nomogram using the negative likelihood ratio for ultrasound-guided vacuum-assisted biopsy is shown. A typical woman with a mammogram described as BI-RADS 4 pre-biopsy has an approximate 30% probability of having a malignant tumor. The dotted blue line in the nomogram can be drawn with a straight-edge from 30% on the left side of the figure, through the negative likelihood ratio of 0.04, and continue in a straight line to the right side of the figure to 2%, indicating that if this woman has a "benign" finding on her core-needle biopsy her post-biopsy probability of having a malignant tumor is approximately 2%.

Figure 3. Example of a nomogram



Scope and Key Questions

This systematic review was commissioned by the Agency for Healthcare Research and Quality (AHRQ) to address the following Key Questions:

1. In women with a palpable or non-palpable breast abnormality, what is the accuracy of different types of core-needle breast biopsy compared with open biopsy for diagnosis? (*The primary outcomes for determination of accuracy are missed cancers [the false negative rate, or sensitivity] and the underestimation rate).*

1a. What factors associated with the patient and her breast abnormality influence the accuracy of different types of core-needle breast biopsy compared with open biopsy for diagnosis of a breast abnormality?

Patient and lesion-associated factors include, but may not be limited to:

Age, characteristics of lesion on mammography or other imaging, breast density, tissue type(s) and architecture of breast lesion, location of breast lesion, or other patient clinical health issues that may affect biopsy (i.e., clotting disorder).

1b. What factors associated with the procedure itself influence the accuracy of different types of core-needle breast biopsy compared with open biopsy for diagnosis of a breast abnormality?

Procedure-related factors include, but may not be limited to:

Equipment used, gauge of core-needle needle used, number of cores, area/amount of specimen obtained, use of vacuum, specific device used, and use of imaging guidance (e.g., MRI, US, stereotactic techniques).

1c. What clinician and facility factors influence the accuracy of core-needle breast biopsy compared with open biopsy for diagnosis of a breast abnormality?

Clinician and facility factors include, but may not be limited to:

Training and experience of clinicians performing the diagnostic procedure and interpreting breast specimen (e.g., specialized breast team, pathologist), annual volume of each procedure performed at facility, geographic location (where in country/world), practice setting (e.g., group, solo), facility setting (e.g., office, ambulatory surgical center, hospital)

2. In women with a palpable or non-palpable breast abnormality, what are the harms associated with core-needle breast biopsy compared to the open biopsy technique in the diagnosis of breast cancer? (*The primary outcomes for determination of harms are inconclusive findings and the re-biopsy rate, dissemination of cancerous cells along needle track, complications, patient centered outcomes including satisfaction, quality of life metrics, time to recover, use of pain medications and subsequent false positive and false negative rate on mammography.*)

2a. What factors associated with the patient and her breast abnormality influence the harms of core-needle breast biopsy compared with the open biopsy technique in the diagnosis of a breast abnormality?

Patient and lesion-associated factors include, but may not be limited to:

Age, characteristics of lesion on mammography or other imaging, breast density, tissue type(s) and architecture of breast lesion, location of breast lesion, or other patient clinical health issues that may affect biopsy (i.e., clotting disorder).

2b. What factors associated with the procedure itself influence the harms of core-needle breast biopsy compared with the open biopsy technique in the diagnosis of a breast abnormality?

Procedure-related factors include, but may not be limited to:

Equipment used, gauge of core-needle needle used, number of core samples, area/amount of specimen obtained, use of vacuum, specific device used, and use of imaging guidance (e.g., MRI, US, stereotactic techniques).

2c. What clinician and facility factors influence the harms of core-needle breast biopsy compared with the open biopsy technique for diagnosis of a breast abnormality?

Clinician and facility factors include, but may not be limited to:

Training and experience of clinicians performing the diagnostic procedure and interpreting breast specimen (e.g., specialized breast team, pathologist), annual volume of each procedure performed at facility, geographic location (where in country/world), practice setting (e.g., group, solo), facility setting (e.g., office, ambulatory surgical center, hospital)

3. How do open biopsy and various core-needle techniques differ in terms of patient preference, availability, costs, availability of qualified pathologist interpretations, and other factors that may influence choice of particular technique?

This report focuses on the use of core-needle biopsies to evaluate suspected cancer confined to the breast. Fine-needle aspiration is outside the scope of this report. Other uses of biopsy for diagnosing and managing breast cancer, or any other issue not mentioned in the Key Questions, are outside the scope of this report.

Chapter 2. Methods

Topic Development

In response to Section 1013 of the Medicare Modernization Act, AHRQ requested an evidence report to synthesize the evidence on the comparative effectiveness of core needle and open surgical biopsy for diagnosis of breast cancer. The topic was nominated in a public process. The Scientific Resource Center (SRC) for the AHRQ Effective Health Care Program recruited a technical expert panel (TEP) to give input on key steps including the selection and refinement of the questions to be examined. The expert panel membership is provided in Appendix A.

Upon AHRQ approval, the draft Key Questions were posted for public comment. After receipt of public commentary, the SRC finalized the Key Questions and submitted them to AHRQ for approval. These Key Questions are presented in the Scope and Key Questions section of the Introduction.

Our EPC created a work plan for developing the evidence report. The process consisted of working with AHRQ, the SRC, and the technical experts to outline the report's objectives, performing a comprehensive literature search, abstracting data, constructing evidence tables, synthesizing the data, and submitting the report for peer review.

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design and/or methodologic approaches do not necessarily represent the views of individual technical and content experts.

Search Strategy

The medical literature was searched from December 1990 through November 10, 2008, and the PubMed and EMBASE searches were updated to September 11, 2009. The full strategy is provided in Appendix B. In brief, we searched 14 external and internal databases, including PubMed and EMBASE, for clinical trials addressing the Key Questions. To supplement the electronic searches, we also examined the bibliographies/reference lists of included studies, recent narrative reviews, and scanned the content of new issues of selected journals and selected relevant gray literature sources.

Study Selection

We selected the studies that we consider in this report using *a priori* inclusion criteria. Some of the criteria we employed are geared towards ensuring that we used only the most reliable evidence. Other criteria were developed to ensure that the evidence is not derived from atypical patients or interventions, and/or outmoded technologies.

Studies of diagnostic test performance compare results of the experimental test to a reference test. The reference test is intended to measure the "true" disease status of each patient. It is important that the results of the reference test be very close to the truth, or the performance of the experimental test will be poorly estimated. For the diagnosis of breast cancer, the "gold standard" reference standard test is open surgical biopsy. However, an issue with the use of open surgical biopsy as the reference standard in large cohort studies of screening-detected breast

abnormalities is the difficulty of subjecting women with probably benign lesions to open surgical biopsy. Furthermore, restricting the evidence base to studies that used open surgery as the reference standard for all enrolled subjects would eliminate the majority of the evidence. Therefore, we have chosen to use a combination of clinical and radiologic followup as well as open surgical biopsy as the reference standard for our analysis.

For Key Question 1 we used the following formal criteria to determine which studies would be included in our analysis. Many of our inclusion criteria for Key Question 1 were intended to reduce the potential for spectrum bias. Spectrum bias refers to the fact that diagnostic test performance is not constant across populations with different spectrums of disease. For example, patients presenting with severe symptoms of disease may be easier to diagnose than asymptomatic patients in a screening population; and a diagnostic test that performs well in the former population may perform poorly in the latter population. The results of our analysis are intended to apply to a general population of women at average risk of breast cancer participating in routine breast cancer screening programs (mammography, clinical examination, and self-examination programs) and therefore many of our inclusion criteria are intended to eliminate studies that enrolled populations of women at very high risk of breast cancer due to family history, or populations of women at risk of recurrence of a previously diagnosed breast cancer.

1. The study must have directly compared core-needle biopsy to open surgery or patient followup for six months or longer in the same group of patients.
   Although it is possible to estimate diagnostic accuracy from a two-group trial, the results of such indirect comparisons must be viewed with great caution. Diagnostic cohort studies, wherein each patient acts as her own control, are the preferred study design for evaluating the accuracy of a diagnostic test.[20] Retrospective case-control studies and case reports were excluded. Retrospective case-control studies have been shown to overestimate the accuracy of diagnostic tests, and case reports often report unusual situations or individuals that are unlikely to yield results that are applicable to general practice.[20,21] Retrospective case studies (studies that selected cases for study on the basis of the type of lesion diagnosed by core-needle biopsy) were also excluded because the data such studies report cannot be used to calculate the overall diagnostic accuracy of core-needle biopsy. Studies may have performed open surgical procedures on all patients, or may have performed open surgical biopsy on some patients and followed the other patients with clinical examination and mammograms for at least six months.

2. The study enrolled female human subjects.
   Animal studies or studies of "imaging phantoms" are outside the scope of the report. Studies of breast cancer in men are outside the scope of the report.

3. The study must have enrolled patients referred for biopsy for the purpose of primary diagnosis of a breast abnormality.
   Studies that enrolled women who were referred for biopsy after discovery of a possible breast abnormality by screening mammography or routine physical examination were included. Studies that enrolled subjects that were undergoing biopsy for any of the following purposes were excluded as being out of scope of the report: breast cancer staging, evaluation for a possible recurrence of breast cancer, monitoring response to treatment, evaluation of the axillary lymph nodes, evaluation of metastatic or suspected metastatic disease, or diagnosis of types of cancer other than primary breast cancer.

Studies that enrolled patients from high-risk populations such as BRCA1/2 mutation carriers are also out of scope. If a study enrolled a mixed patient population and did not report data separately, it was excluded if more than 15% of the subjects did not fall into the "primary diagnosis of women at average risk presenting with an abnormality detected on routine screening" category.

4. Fifty percent or more of the subjects must have completed the study.
   Studies with extremely high rates of attrition are prone to bias and were excluded.

5. Study must be published in English.
   Moher et al. and Holenstein et al. have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn.[22,23] *Although we recognize the possibility that requiring studies to be published in English could lead to bias, it is insufficiently likely that we cannot justify the time and cost of translations.*

6. Study must be published as a peer-reviewed full article. Meeting abstracts were not included.
   Published meeting abstracts have not been peer-reviewed and often do not include sufficient details about experimental methods to permit one to verify that the study was well designed.[24,25] *In addition, it is not uncommon for abstracts that are published as part of conference proceedings to have inconsistencies when compared to the final publication of the study, or to describe studies that are never published as full articles.*[26-30]

7. The study must have enrolled 10 or more individuals per arm.
   The results of very small studies are unlikely to be applicable to general clinical practice. Small studies are unable to detect sufficient numbers of events for meaningful analyses to be performed, and are at risk of enrolling unique individuals.

8. When several sequential reports from the same patients/study are available, only outcome data from the most recent report were included. However, we used relevant data from earlier and smaller reports if the report presented pertinent data not presented in the more recent report.

9. Studies of biopsy instrumentation that are no longer commercially available were excluded.
   The ABBI device, the MIBB device, and SiteSelect have been discontinued by their manufacturers. Studies of the accuracy and harms related to the use of these devices are no longer clinically relevant.

To address Question 2, we recorded any harms information reported in the studies included to address Question 1. In addition, we collected any articles, regardless of design, that addressed part of Question 2, namely the dissemination of cancer cells by the biopsy procedure. To address Question 3, we consulted a variety of information sources, including published literature, cost-effectiveness analyses, evidence-based clinical practice guidelines, published expert panel consensus statements, and consultations with experts. We did not use formal

inclusion criteria for Question 3 due to the nature of the question; instead, we approached the question as an "opinion/discussion" type of question.

To address the accuracy of open surgical biopsy, we first searched for clinical studies that performed open surgical biopsy, followed patients for six months or longer, and met the above listed inclusion criteria. However, we identified no clinical studies that met the inclusion criteria, so we searched for systematic and narrative reviews that addressed the accuracy and harms of open surgical biopsy.

The abstracts of articles identified by the literature searches were screened in duplicate for possible relevance by three research assistants. The first fifty abstracts screened by each research assistant were also screened in duplicate by the lead research analyst, and all exclusions at the abstract level were approved by the lead research analyst. The full-length articles of studies that appeared relevant at the abstract level were then obtained and three research assistants examined the articles in duplicate to see if they met the inclusion criteria. All conflicts were resolved by the lead research analyst. The excluded articles and primary reason for exclusion are shown in Appendix C.

Data Abstraction

Standardized data abstraction forms were created and data was entered by each reviewer into the SRS© 4.0 database (see Appendix D). Three research assistants abstracted the data. The first fifty articles were abstracted in duplicate. All conflicts were resolved by the lead research analyst.

Study Quality Evaluation

We used an internal validity rating scale for diagnostic studies to grade the internal validity of the evidence base (Table 2). This instrument is based on a modification of the QUADAS instrument.[31] Each question in the instrument addresses an aspect of study design or conduct that can help to protect against bias. Each question can be answered "yes", "no", or "not reported," and each is phrased such that an answer of "yes" indicates that the study reported a protection against bias on that aspect. A summary quality score was computed in order to reduce the subjectivity of the assessment of the potential for bias present in the evidence base. A summary score was computed with each "yes" given a +1, each "no" a -1, and each "not reported" a zero. As all of the factors captured by the questions on the quality instrument were thought to be of equal importance for this topic, no weighting was utilized in computing the summary score. This summary score was then normalized[a] to a scale from 0 to 10, with the lower the score the greater the risk that the study was affected by biases. Consequently, a study employing all 14 features would score +10, a study employing none would score 0, and a study simply not reporting any of these features would score 5, thus acknowledging that published studies may not provide information on all study procedures that were actually carried out.

To evaluate the overall quality of the evidence base for each conclusion, we computed the median quality score of the studies contributing to that conclusion. An evidence base with a median score higher than 8.4 was considered to be of high quality; an evidence base with a median score 8.4 or less but greater than 6.7 was considered to be of moderate quality; an evidence base with a median score 6.7 or less but greater than 5.0 was considered to be of low

[a] Formula:((raw score +14)/28)*10

quality; and an evidence base with a median score less than 5.0 was considered to be of insufficient quality. Internal validity assessment findings are summarized for each outcome in the Results section. Responses to the questions in the quality assessment instrument for each study are presented in the Evidence Tables in the Appendix.

Table 2. Quality assessment instrument

1. Was patient recruitment either consecutive or random?
2. Were more than 85% of the patients approached for recruitment enrolled in the study?
3. Were the patient inclusion/ exclusion criteria consistently applied to all patients?
4. Was the study free from obvious spectrum bias? Obvious spectrum bias was defined as more than 40% or less than 10% of the breast lesions were diagnosed as malignant; and/or the mean or median age of the enrolled population was less than 50 or greater than 70.
5. Was the study prospective in design?
6. Was a complete set of data reported for at least 85% of enrolled lesions?
7. Were the patients assessed by the reference standard (open surgical procedure) regardless of the initial biopsy results?
8. Were patients assessed by a reference standard regardless of the biopsy results?
9. Was funding for this study provided by a source that doesn't have an obvious financial interest in the findings of the study?
10. Did the study account for inter-reader/scorer differences?
11. Were the reader(s) of the biopsies blinded to the results of the reference standard?
12. Were readers of the reference standard blinded to the results of the biopsy?
13. Were the readers of the biopsy blinded to all other clinical information?
14. Were readers of the reference standard blinded to all other clinical information?

Strength of Evidence

The strength of evidence supporting each major conclusion was graded as High, Moderate, Low, or Insufficient. The grade was developed by considering various important domains as suggested in the CER Draft Methods Guide and in accordance with a strength and stability of evidence grading system developed by ECRI Institute.[32] Four domains were evaluated: the quality (potential risk of bias, or "internal validity") of the evidence base, the size of the evidence base, the consistency (agreement across studies) of the findings, and the robustness of the findings (as determined by sensitivity analysis). The domain of "directness" was incorporated into our analytic framework, but not into the grade, as downstream patient health outcomes are rarely reported in diagnostic studies. The domain of "precision" was incorporated into our assessment of the size of the evidence base.

The domain considered to be of overriding importance for this topic was the potential for bias in the evidence base. The potential for bias was measured by the quality of the evidence as described above. The quality rating was considered to be the highest strength of evidence grade that could be achieved for each conclusion. The other domains were evaluated as either "Sufficient" or "Insufficient," and ratings of "Insufficient" for other domains caused a

downgrading of the strength of evidence grade. Further details about grading the strength of evidence may be found in Appendix G.

Because of the nature of Question 3 and the sources of information used to address it, we did not draw many formal evidence-based conclusions for this question, nor, in most cases, did we attempt to rate the quality of the studies or grade the strength of the evidence. For one conclusion for Key Question 3 we considered the consistency, robustness, and strength of association between the type of biopsy and the outcome to be sufficient to support an evidence-based conclusion.

Applicability

The issue of applicability was chiefly addressed by excluding studies that enrolled patient populations that were not a general population of asymptomatic women participating in routine breast cancer screening programs. We defined this population as women at average risk of breast cancer participating in routine breast cancer screening programs (including mammography, clinical examination, and self-examination). We excluded studies that enrolled women who were referred for biopsy for the purpose of: staging of already diagnosed breast cancers; evaluation of the axillary lymph nodes; evaluation for metastatic or suspected metastatic disease; evaluation of recurrent or suspected recurrent disease; and studies that enrolled women thought to be at very high risk of breast cancer due to family history or carriers of BRCA mutations. We also excluded studies of biopsy instrumentation that are no longer commercially available on the grounds that the data reported is no longer applicable to clinical practice.

To verify that the evidence base enrolled a "typical" population we examined the prevalence of breast cancers diagnosed. The prevalence of cancers in the general population sent for breast biopsy (in the U.S.) has been reported to be around 23%.[15] If our evidence base were indeed typical for patients in the U.S., we would expect to see a similar prevalence of breast cancers.

Data Analysis and Synthesis

Several key assumptions were made: (1) the "reference standard," open surgical biopsy and/or clinical and radiologic followup for at least six months, was 100% accurate; (2) the pathologists diagnosing the open surgical biopsy results were 100% accurate in diagnosing the material submitted to them; and (3) core-needle diagnoses of malignancy (invasive or in situ) that could not be confirmed by an open surgical procedure were assumed to have been correct diagnoses where the lesion had been completely removed by the core-needle biopsy procedure.[33] In addition, the majority of studies reported data on a per-lesion rather than a per-patient basis, and therefore we analyzed the data on a per-lesion basis assuming that statistical assumptions of data independence were not being violated.

We performed two primary types of analyses - a standard diagnostic accuracy analysis and an analysis of underestimation rates. For the diagnostic accuracy analysis,

- true negatives were defined as lesions diagnosed as benign on core-needle biopsy that were found to be benign by the reference standard;
- false negatives were defined as lesions diagnosed as benign on core-needle biopsy that were found to be malignant (invasive or in situ) by the reference standard;

- true positives were defined as lesions diagnosed as malignant (invasive or in situ) on core-needle biopsy as well as "high risk" lesions that were found to be malignant (invasive or in situ) on the reference standard
- false positives were defined as lesions diagnosed as "high risk"(most commonly ADH lesions) on core-needle biopsy that were found not to be malignant (invasive or in situ) by the reference standard (see Table 3).

We meta-analyzed the data reported by the studies using a bivariate mixed-effects binomial regression model as described by Harbord et al.[34] All such analyses were computed by the STATA 10.0 statistical software package using the "midas" command.[35] The summary likelihood ratios and Bayes theorem were used to calculate the post-test probability of having a benign or malignant lesion. In cases where a bivariate binomial regression model could not be fit we meta-analyzed the data using a random-effects model and the software package Meta-Disc.[36] Meta-regressions were also performed with the Meta-Disc software package.

Diagnostic tests all have a trade-off between minimizing false-negative and minimizing false-positive errors. False-positive errors that occur on core-needle biopsy are not considered to be as clinically relevant as false-negative errors. Women who experience a false-positive error will be sent for an additional biopsy procedure, and may suffer anxiety and minor temporary complications. However, women who experience a false-negative error may die from a delayed cancer diagnosis. In addition, because all "positive" diagnoses of malignancy on core-needle biopsy are assumed to be correct, the "true" false positive rate is artificially reduced towards 0%. Thus false-positive errors, and diagnostic test characteristics that evaluate the impact of false-positive errors (specificity, positive predictive value, positive likelihood ratio), are not particularly relevant for evaluating this technology.

We focused on measures that evaluate the extent of false-negative errors: sensitivity and negative likelihood ratio. A biopsy method with a very high sensitivity misses very few cancers. Negative likelihood ratios can be used along with Bayes' theorem to directly compute an individual woman's risk of having a malignancy following a "benign" diagnosis on core-needle biopsy. In general, the smaller the negative likelihood ratio the more accurate the diagnostic test is in predicting the absence of disease. However, each individual woman's post-test risk varies by her pre-test risk of malignancy. Simple nomograms are available for in-office use that allow clinicians to directly read individual patients' post-test risk off a graph without having to go through the tedium of calculations. Negative predictive value is another commonly used measure of false-negative errors; however, negative predictive values are specific to specific populations of women. They can be used to predict how many women in that particular population do not have a malignancy following a "benign" diagnosis on core-needle biopsy. Negative predictive values vary by the prevalence of disease in each specific population and should not be applied to other populations with different prevalences of disease.

The second type of analysis we performed was an analysis of underestimation rates. Lesions diagnosed as DCIS by core-needle biopsy that were found to be invasive by the reference standard were counted as underestimates. Similarly, "high risk" (most commonly ADH lesions) that were found to be malignant (in situ or invasive) by the reference standard were counted as underestimates (see Table 4). The underestimation rate was then calculated as the number of underestimates per number of DCIS (or "high risk") diagnoses and expressed as a percentage (the percentage of DCIS or ADH diagnoses that were underestimates). We meta-

analyzed the underestimation rates with a random-effects model using the CMA software package.[37]

We meta-analyzed any other types of outcomes with a random-effects model using the CMA software package.[37] We did not assess the possibility of publication bias because statistical methods developed to assess the possibility of publication bias in treatment studies have not been validated for use with studies of diagnostic accuracy.[38,39]

Table 3. Definitions of diagnostic test characteristics

		Reference standard results (open surgery or followup)	
		Malignant (invasive or in situ tumor)	**Benign**
Core-needle biopsy results	**Malignant (invasive or in situ)**	True positive	True positive[a]
	ADH or other "high risk" lesions type	True positive	False positive
	Benign	False negative	True negative

[a.] Most authors assumed malignant diagnoses on core-needle were true positives even if no tumor was identified by surgical excision.
Sensitivity = (true positives/ (true positives + false negatives))*100
Negative likelihood ratio = (false negatives/(true positives + false negatives)/(true negatives/false positives + true negatives)

Table 4. Definitions of underestimation rates

		Reference standard results (open surgery or followup)		
		Malignant (invasive)	**Malignant (in situ)**	**Benign**
Core-needle biopsy results	**DCIS**	Underestimation	Not underestimated	Not underestimated
	ADH or other "high risk" lesion type	Underestimation	Underestimation	Not underestimated

DCIS underestimation = (number cases diagnosed as DCIS on core-needle biopsy that were found to be invasive cancer by the reference standard)/ (total number cases diagnosed as DCIS on core-needle biopsy)*100
ADH underestimation = (number cases diagnosed as ADH on core-needle biopsy that were found to be invasive or in situ cancer by the reference standard)/ (total number cases diagnosed as ADH on core-needle biopsy)*100

Peer Review and Public Commentary

A draft of the completed report was sent to the peer reviewers, the representatives of the AHRQ, and the Scientific Resource Center. The draft report was posted to a Web site for public comment. In response to the comments of the peer reviewers and the public, revisions were made to the evidence report, and a summary of the comments and their disposition was submitted to AHRQ. Peer reviewer comments on a preliminary draft of this report were considered by the EPC in preparation of this final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

Chapter 3. Results

Question 1. In women with a palpable or non-palpable breast abnormality what is the accuracy of different types of core-needle breast biopsy compared with open biopsy for diagnosis?

Evidence Base

Our literature searches identified 1,224 potentially relevant articles. After review of the abstracts, the full-length articles of 589 of these studies were obtained and examined in full. Of these, 107 studies met the inclusion criteria for Key Question 1. The excluded studies and primary reason for exclusion are shown in Appendix C. The studies are briefly described in Table 5. Full Full details about the included studies, the enrolled patients, the biopsy methods, and the characteristics of the breast lesions are shown in the evidence tables in Appendix E.

Thirty-five of the 107 studies were prospective in design. Forty-nine were conducted in the United States. Ninety-three were carried out in general hospitals. A total of 57,088 breast lesions were enrolled in the 107 studies. The overall quality of the entire evidence base was rated as low (median score 6.1, range 3.6 to 8.2); see Table 5 for details.

Accuracy of Open Surgical Biopsy

Obtaining information on the accuracy of open surgical biopsy was, not surprisingly, difficult. Practically all authors and experts assume that open surgical biopsy is 100% accurate. We did not identify any clinical studies of open surgical biopsy that met our inclusion criteria (see Methods section).

We identified an article by Antley et al. 1998 that reviewed the accuracy of open surgical biopsy.[40] Antley et al. reviewed the available information (published literature as well as patient charts available in the author's medical center) on the accuracy of open surgical biopsy and concluded that open surgical biopsy has been reported to miss 1 to 2% of breast cancers (a sensitivity of 98% or greater). This estimate is based upon a re-review of archived open biopsy material by a second pathologist, the charts reviewed by Antley et al., a study of cases of benign results on biopsy after a very suspicious mammogram, and expert opinion.[41-43]

We did not identify any information on estimates of underestimation rates for open surgical biopsy. However, underestimations are generally thought to be due to failure to sample all important areas of a lesion. For example, a lesion may contain a foci of carcinoma within a cluster of atypical cells. Biopsy samples collected by core-needle may fail to sample any of the carcinoma cells, leading to an underestimation. Because open surgical biopsy samples most or all of the lesion, in theory underestimations should not occur. Therefore, we have assumed that open surgical biopsy has a zero, or close to zero, underestimation rate.

Accuracy of Core-Needle Biopsy

We attempted to fit a bivariate binomial regression model to the data reported by all 107 studies but the data were too heterogeneous to allow a valid model to be fit. Due to obvious differences across studies of biopsy methods and enrolled patient populations, we did not perform further analyses on the full set of data. In the following analyses we have grouped the studies by the type of core-needle biopsy used in the study. The analyses are summarized in

Figure 1 A through Figure 4 D in the Executive Summary and in Table 6 and Table 7. Full details of the analyses and reported data are provided in Appendix F.

Freehand Core-Needle Biopsies

Five studies reported data on the accuracy of non-guided, i.e., freehand, core-needle biopsies performed with automated biopsy gun devices.[44-48] We fit a bivariate binomial model. There was very little heterogeneity in the data (I^2 = 6.95%). The summary sensitivity was 85.8% (95% CI: 75.8 to 92.1%) and the summary negative likelihood ratio was 0.143 (95% CI: 0.082 to 0.250). This ratio indicates that for a woman with a pre-test probability of malignancy of 30%, her probability of having malignancy after a negative freehand core-needle biopsy would be 5.8%. A pre-test probability of 30% was chosen because the average woman undergoing core-needle biopsy has been categorized as BI-RADS 4 before undergoing the biopsy, and such women have an approximate overall prevalence of malignancy of 30%.[15] We have used the 30% pre-test probability in the analyses that follow for the same reason. However, it is important to realize that each individual woman's pre-test probability may vary from this estimate.

None of the studies reported underestimation rates. Because there were only five studies we did not perform any sub-group or meta-regression analyses.

Cusick et al. noted that smaller lesions (less than 2 cm in diameter) were more likely to be misdiagnosed.[48] In contrast, Barreto et al. commented that neither tumor size nor patient age affected the accuracy of the procedure; however, tumors located in the right breast were much more likely to receive false-negative diagnoses, perhaps due to the fact that the persons performing the biopsy procedures were right handed.[47] Barreto et al. also noted that operator inexperience was a key factor in misdiagnoses.[47] The apparent difference in conclusions about the impact of tumor size on biopsy accuracy is probably due to the fact that the tumors in the study by Barreto et al. were all larger than 2 cm in diameter.

We graded the conclusions from this evidence as Low. The quality of the evidence base was rated as Low (median score 5.7), but quantity, consistency, and robustness were all rated as Sufficient.

Ultrasound Guided Automated Gun Core-Needle Biopsies

Sixteen studies of 7,124 biopsies used ultrasound guidance and an automated biopsy gun.[49-64] We could not fit a bivariate binomial model due to heterogeneity. The random-effects model found a summary sensitivity of 97.7% (95% CI: 97.2 to 98.2%) and a summary negative likelihood ratio of 0.030 (95% CI: 0.022 to 0.040). This ratio indicates that for a woman with a pre-test probability of malignancy of 30%, her probability of having malignancy after a negative ultrasound-guided automated gun core-needle biopsy would be 1.3%. Twelve of the sixteen studies reported data on atypia underestimation rates.[49,51-53,56-61,63,64]; the summary atypia underestimation rate was 29.2% (23.4 to 35.9%). Twelve studies reported data on DCIS underestimation rates.[49,51-53,55-61,64] the summary DCIS underestimation rate was 35.5% (27.1 to 45.0%). We graded the conclusions from this evidence as Low. The quality of the evidence base was rated as Low (median score 6.1), but quantity, consistency, and robustness were all rated as Sufficient.

We then proceeded to explore factors that might affect the accuracy of the biopsies by performing meta-regressions. We only performed meta-regressions if all of the studies reported information about the factor being analyzed and at least three studies were different from the rest of the studies for that factor.

Patient and Breast Lesion Factors

The studies reported insufficient information about characteristics of the lesions or the patients to explore the impact of these factors on the accuracy of the biopsies.

Biopsy Procedure Factors

Only seven of the studies reported information about patient position during the procedure, and six of these reported the patients were supine[49,51,56,60,62,63] while the seventh reported the patients were seated.[58] All but two of the studies reported using a 14G needle; one of these two studies used an 18G needle, and one used different sizes of needles for different patients.[59,62]

Three of the fifteen studies verified all core-needle findings with surgery[50,58,62] (the rest used a combination of surgery and patient followup), and six of the studies did not follow all patients for at least two years.[52,53,55,57,60,63] Meta-regression did not find a statistically significant impact of methods of verification of biopsy on the accuracy of the biopsies.

One study, de Lucen et al., evaluated the impact of number of cores taken on the accuracy of the procedure. The authors of the study reported that taking more than 2 cores did not improve the accuracy of the procedure.[50] However, Fishman et al. reported that taking more than 2 cores did improve the accuracy of the biopsy, with 4 cores being the optimal number.[55] Fishman et al.'s conclusion was based on one case of DCIS that would have been missed if fewer than 4 cores had been taken; the other 13 tumors identified in the study would have been correctly diagnosed if only 2 cores had been taken. de Lucen et al.'s conclusion was based on the fact that the six tumors (out of a total of 101 tumors identified in the study) that were falsely diagnosed as benign by core-needle biopsy would not have been correctly diagnosed even if up to six cores were taken.

Clinician and Facility Factors

All but one of the studies were performed in general hospitals. The studies were conducted in settings around the world; meta-regression did not find a statistically significant effect of geographic location on the accuracy of the biopsies. Most of the studies did not report data about the training or experience of the persons performing the biopsies.

Stereotactic-Guided Automated Gun Core-Needle Biopsies

Thirty-three studies of 7153 biopsies used stereotactic guidance and an automated biopsy gun.[65-97] We were able to fit a bivariate binomial model. The summary sensitivity was 97.8% (95% CI: 95.8 to 98.9%) and the summary negative likelihood ratio was 0.022 (95% CI: 0.012 to 0.043). This ratio indicates that for a woman with a pre-test probability of malignancy of 30%, her probability of having malignancy after a negative stereotactically-guided automated gun core-needle biopsy would be 0.9%. Twenty-six of the 33 studies reported data on atypia underestimation rates.[65-69,71,73-90,94,96] and 17 reported data on DCIS underestimation rates.[65-68,73,75,76,78-81,85,86,89-92] The atypia underestimation rate was 43.5% (95% CI: 35.7 to 51.7%) and the DCIS underestimation rate was 24.4% (95% CI: 18.0 to 32.1%). We graded the conclusions from this evidence as Low. The quality of the evidence base was rated as Low (median score 6.1), but quantity, consistency, and robustness were all rated as Sufficient.

We then proceeded to explore factors that might affect the accuracy of the biopsies by performing meta-regression. We only performed meta-regressions if all of the studies reported

information about the factor being analyzed and at least three studies were different from the rest of the studies for that factor.

Patient and Breast Lesion Factors

Koskela et al. reported zero false-negatives out of 97 procedures performed on lesions detected as masses on mammography but 4 false-negatives out of 108 procedures performed on lesions with microcalcifications.[66] Walker et al. reported that the sensitivity of core-needle biopsy was much lower for microcalcifications than for any other type of lesion.[85]

The majority of the studies appeared to have enrolled patients with only non-palpable lesions but many of the studies did not report on the palpability of the lesions. The studies reported insufficient information about other characteristics of the lesions or the patients to explore the impact of these factors on the accuracy of the biopsies.

Biopsy Procedure Factors

All but three of the studies used 14G needles,[78,79,92] and meta-regression did not find a statistically significant impact of needle size on biopsy accuracy. Twenty-two of the studies reported that the patients were prone,[65,67,68,70,73,75,76,80,82-84,86-96] three reported the patients were seated,[66,69,72] one reported the patients were in the decubitus position,[77] one reported patients were either prone or seated,[81] but six did not report information about patient positioning.[71,74,78,79,85,97]

Eight of the studies verified all core-needle findings with surgery[68,72,73,79,94-97] (the rest used a combination of surgery and patient followup), and 22 of the studies did not follow all patients for at least two years.[66,67,69,70,74-78,80-87,89-93] Meta-regression did not find a statistically significant impact of methods of verification of biopsy on the accuracy of the biopsies.

Koskela et al. reported that more than three cores need to be taken from lesions before an accurate diagnosis can be made.[66]

Clinician and Facility Factors

Twenty-nine of the studies were conducted at a single center (the other four were multi-center studies[65,68,70,79]). Twenty-six of the studies were conducted in general hospitals,[65-69,71-76,78,81-83,85-87,89-92,94-97] four were conducted in free-standing dedicated cancer centers,[77,80,88,93] one was conducted in a breast cancer screening clinic,[84] and one was conducted in multiple centers of different types.[70] Twenty of the studies were conducted within the United States[70,75,76,79-83,86-97] and the rest were scattered worldwide. Meta-regressions did not find that any of these factors had a statistically significant impact on biopsy accuracy.

The majority of studies reported that radiologists performed the biopsies, but many studies did not report information about the training of the operators. Very few of the studies reported the degree of experience of the operators or their caseloads.

Ultrasound-Guided Vacuum-Assisted Core-Needle Biopsies

Seven studies of 507 biopsies used ultrasound guidance and a vacuum-assisted device to perform breast biopsies.[56,98-103] There was no significant heterogeneity in the data ($I^2 = 0.0\%$). We fit a bivariate binomial model to the data. The summary sensitivity was 96.5% (95% CI: 81.2 to 99.4%) and the summary negative likelihood ratio was 0.036 (95% CI: 0.006 to 0.212). This ratio indicates that for a woman with a pre-test probability of malignancy of 30%, her probability of having malignancy after a negative vacuum-assisted ultrasound-guided core-needle biopsy

would be 1.5%. The studies reported no cases of atypia underestimation and only a single case of DCIS underestimation.[56] We graded the conclusions from this evidence as Low. The quality of the evidence base was rated as Low (median score 5.9), but quantity, consistency, and robustness were all rated as Sufficient.

Due to the lack of heterogeneity in the data, we did not perform any meta-regressions to explore the impact of factors on accuracy. The following differences between studies do not appear to affect accuracy.

Patient and Breast Lesion Factors

The studies reported very little information about the patients or lesions.

Biopsy Procedure Factors

All of the studies verified core-biopsy results by a combination of open surgery and patient followup. Only one of the seven studies followed all patients for at least two years.[98]

Five of the studies used the Mammotome device with an 11G needle,[56,99,101-103] one study used a VACORA device with a 10G needle,[98] and one study did not report information about the device or needle gauge.[100] Four of the studies reported the patients were supine[56,100,102,103] and the others did not report details of patient positioning.

Clinician and Facility Factors

Two of the studies were conducted in free-standing cancer centers[101,103] and the others were performed in general hospitals. The studies were conducted in many different countries worldwide. The studies generally did not report information on operator training or experience.

Stereotactic-Guided Vacuum-Assisted Core-Needle Biopsies

Twenty-two studies of 7,153 biopsies used stereotactic guidance and a vacuum-assisted device to perform core-needle biopsies.[76,80,104-123] We were able to fit a bivariate binomial model. The summary sensitivity was 99.2% (95% CI: 98.1 to 99.6%) and the summary negative likelihood ratio was 0.009 (95% CI: 0.004 to 0.021). This ratio indicates that for a woman with a pre-test probability of malignancy of 30%, her probability of having malignancy after a negative vacuum-assisted stereotactically-guided core-needle biopsy would be 0.4%. All of the studies reported information about atypia and DCIS underestimation rates. The summary atypia underestimation rate was 21.7% (95% CI: 17.7 to 26.4%) and the summary DCIS underestimation rate was 12.9% (95% CI: 11.1 to 15.1%). The low DCIS underestimation rate may affect treatment planning. The surgeon performing the followup open surgical procedure can be reasonably confident that a malignant tumor is not present, and therefore may plan to remove the lesion using a breast-conserving approach, and may decide to not sample the axillary lymph nodes. Some women and physicians may decide that the ADH underestimation rate is low enough to safely substitute surveillance for an open biopsy procedure after diagnosis of ADH on core-needle biopsy. We graded the conclusions from this evidence as Low. The quality of the evidence base was rated as Low (median score 6.1), but quantity, consistency, and robustness were all rated as Sufficient.

We then proceeded to explore factors that might affect the accuracy of the biopsies by performing meta-regressions. We only performed meta-regressions if all of the studies reported information about the factor being analyzed and at least three studies were different from the rest of the studies for that factor.

Patient and Breast Lesion Factors

Two studies reported that stereotactic-guided vacuum-assisted core-needle biopsy was equally accurate for lesions with microcalcifications and lesions detected as masses on mammography.[110,117]

Nine of the 21 studies reported that all of the lesions were non-palpable[76,104,108,110-112,114-116] but the other studies reported no information on palpability of enrolled lesions. The studies reported insufficient information about characteristics of the lesions or the patients to explore the impact of these factors on the accuracy of the biopsies.

Biopsy Procedure Factors

All 21 studies used the Mammotome device either exclusively or in part. Seventeen of the studies used an 11G needle,[80,104-114,117-120,122] two used a 14G needle,[76,116] one used either a 14G or an 11G needle,[121] and one did not report the size of the needle.[115] All but one of the studies used a combination of open surgery and patient followup to verify the results of the biopsies, and it used open surgery on all patients.[117] Only three studies followed all patients for at least two years.[104,110,116] Meta-regression found that method of biopsy verification did not affect the accuracy of the biopsies.

The majority of the studies reported that patients were prone,[76,80,104,105,107-112,114,116-122] two reported that patients were seated,[113,115] and one did not report information about patient positioning.[106]

Lomoschitz et al. reported that 12 cores were necessary for accurate diagnosis and taking more than 12 cores did not improve accuracy.[110]

Clinician and Facility Factors

Only two of the 21 studies were multi-center studies. Three of the studies were conducted in free-standing dedicated cancer centers,[105,106,116] one was conducted in an ambulatory surgical center,[80] and the rest were conducted in general hospitals. Six of the studies were conducted in the USA[76,80,113,114,116,118] and 12 were conducted in Europe.[104,106-112,115,117,120,121] Meta-regression did not find that the type or location of facility affected the accuracy of the biopsies.

Very few of the studies reported any information about the training or experience of the persons performing the biopsies. Pfarl et al. noted that for six of the seven false-negatives that occurred in the study, the biopsy procedure had been performed by an operator who had previously performed fewer than 15 stereotactic-guided biopsies.[117]

MRI-Guided Core-Needle Biopsies

Only one study reported data on the accuracy of MRI-guided biopsies performed with automated biopsy guns.[124]

Perforated Compression Grid Guided Core-Needle Biopsies

Only one study reported data on the accuracy of biopsies performed with automated biopsy guns guided by a perforated compression grid.[125]

Multiple Core-Needle Methods

There were an additional 24 studies that used multiple core-needle biopsy methods in their studies and did not report the data for different biopsy methods separately.[126-149] Some of these studies reported information relevant to this topic as discussed below.

Patient and Breast Lesion Factors

Abdasaleh et al. reported that technical failures were more likely to occur with women with very dense breast tissue.[130]

The authors of Ciatto et al., who used multiple methods of performing core-needle biopsy, reported the percentage of procedures that gave false-negative results by lesion type: 2.7% palpable lesions, 2.2% nonpalpable lesions, 2.3% masses on mammography, 1.4% distortions on mammography, and 2.5% of microcalcifications.[126] Cipolla et al. reported that correspondence between core-needle biopsy and surgical biopsy results was 100% for palpable lesions but only 88% for nonpalpable lesions.[127] Fajardo reported that the sensitivity of core-needle biopsies for nonpalpable lesions and lesions with microcalcifications was 90.7%, much lower than the 97.4% sensitivity of core-needle biopsy for masses detected on mammography.[129]

Biopsy Procedure Factors

Abdasaleh et al. reported that taking two cores instead of one increased the accuracy of the procedure.[130]

Helbich et al. randomly assigned patients to be biopsied in different positions - seated upright, supine, or prone. The accuracy data were not reported separately for each group, but the authors did comment that patient position did not affect the biopsy procedure.[144]

Clinician and Facility Factors

Ciatto et al. reported that sensitivity of core-needle biopsies improved as the operators (radiologists) gained experience, from 88% in the first year of the study to 96% in the last year (eight years overall) of the study.[126]

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Table 5. Studies addressing Key Questions 1 and 2

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Jackman et al. 2009[123]	Stereotactic guidance vacuum-assisted 11G and 14G	5.4	Retrospective	1	General hospital	USA	Partially supported by Biopsys Medical, Inc., and Ethicon Endo-Surgery	1,280	2 years	10.6%
Peters et al. 2008[65]	Stereotactic guidance automated gun 14G	4.6	Retrospective	4	General hospital	Netherlands	NR	948	2 years	5%
Schueller et al. 2008[64]	US guidance automated gun 14G	5.4	Retrospective	1	General hospital	Austria	The authors reported no financial relationship to disclose	1438	2 years	6.0%
Sim and Kei et al. 2008[122]	Stereotactic guidance vacuum-assisted 11G	6.1	Retrospective	1	General hospital	Singapore	NR	105	2 years	12.4%
Tonegutti and Girardi 2008[104]	Stereotactic guidance vacuum-assisted 11G	6.1	Retrospective	1	General hospital	Italy	NR	268	2 years	0%
Youk et al. 2008[49]	US guidance automated gun 14G	4.6	Retrospective	1	General hospital	South Korea	NR	4,359	2 years	44%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Ciatto et al. 2007[126]	Multiple methods	4.6	Retrospective	1	Dedicated breast cancer center	Italy	Funded in part by a National Health and Medical Research Council (NHMRC) grant	4,035	1 year	26%
de Lucena et al. 2007[50]	US guidance automated gun 14G	6.8	Prospective	1	General hospital	Brazil	NR	150	Immediate surgery	0%
Uematsu et al. 2007[105]	Stereotactic guidance vacuum-assisted 11G	7.1	Prospective	1	General cancer center	Japan	NR	100	Mean: 26 months Range: 5 to 44 months	0%
Vag et al. 2007[98]	US guidance vacuum-assisted 10G	6.1	Prospective	1	General hospital	Germany	NR	70	2 years	0%
Chapellier et al. 2006[106]	Stereotactic guidance vacuum-assisted 11G	6.4	Prospective	1	General cancer center	France	NR	318	Range: 4 to 16 months	0%
Cipolla et al. 2006[127]	Multiple methods	6.8	NR	1	General hospital	Italy	NR	426	1 year	0%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Dhillon et al. 2006[107]	Stereotactic guidance vacuum-assisted 11G	7.5	Prospective	1	General hospital	UK	NR	150	Median: 48 months	0%
Bolivar et al. 2005[51]	US guidance automated gun 14G	6.8	Prospective	1	General hospital	Spain	NR	214	2 years	5%
Crystal et al. 2005[52]	US guidance automated gun 14G	6.8	NR	1	General hospital	Israel	NR	715	Median: 39 months Range: 27 to 60 months	0%
Dillon et al. 2005[128]	Multiple methods	4.6	Retrospective	1	General hospital	Ireland	NR	2,427	Median: 24 months Range: 3 to 67 months	19%
Koskela et al. 2005[66]	Stereotactic guidance automated gun 14G	6.1	Prospective	1	General hospital	Finland	Kuopio University Hospital (the center where it was conducted)	213	Mean: 24 months Range: 6 to 39 months	4%
Sauer et al. 2005[53]	US guidance automated gun 14G	5.0	Retrospective	1	General hospital	Germany	NR	962	Mean: 22.2 months Median: 21 months Range: 8 to 36 months	13%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Weber et al. 2005[108]	Stereotactic guidance vacuum-assisted 11G	7.9	Prospective	1	General hospital	Switzerland	NR	225	Median: 2.1 years Range: 0.5 to 4.4 years	15%
Wu et al. 2005[99]	US guidance vacuum-assisted 11G	6.8	NR	1	General hospital	Taiwan	NR	113	1 year	0%
Alonso-Bartolome et al. 2004[100]	US guidance vacuum-assisted 11G	6.8	Prospective	2	General hospital	Spain	NR	102	6 to 12 months	0%
Delle and Terinde 2004[54]	US guidance automated gun 14G	6.8	NR	1	General hospital	Germany	NR	169	2 years	0%
Fajardo et al. 2004[129]	Multiple methods	8.2	Prospective	22	Academic and community practice clinical sites	USA	National Cancer Institute	2,403	2 years	30%
Kettritz et al. 2004[109]	Stereotactic guidance vacuum-assisted 11G	4.6	Prospective	5	General hospital	Germany	NR	2,893	Mean: 25 months Range: 6 to 67 months	22%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Lomoschitz et al. 2004[110]	Stereotactic guidance vacuum-assisted 11G	6.1	Prospective	1	General hospital	Austria	One author partially supported by both Ethicon Endosurgery and Biopsys Medical	100	2 years	0%
Abdsaleh et al. 2003[130]	Multiple methods	7.1	Prospective	1	General hospital	Sweden	NR	180	1 year	21%
Ambrogetti et al. 2003[111]	Stereotactic guidance vacuum-assisted 11G	4.6	Retrospective	1	General hospital	France	NR	364	Mean: 15.8 months Range: 6 to 36 months	35%
Fishman et al. 2003[55]	US guidance automated gun 14G	5.7	Prospective	1	General hospital	USA	NR	73	Mammo-graphic and US followup Median: 21 months Range: 4 to 30 months	33%
Han et al. 2003[67]	Stereotactic guidance automated gun 14G	5.4	Retrospective	1	General hospital	Korea	NR	271	At least 6 months	27%
Kirshenbaum et al. 2003[131]	Multiple methods	5.0	Retrospective	1	General hospital	USA	NR	506	Mean: 2.1 years Range: 3 months to five years.	23%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
March et al. 2003[101]	US guidance vacuum-assisted 11G	5.7	Prospective	2	Dedicated breast cancer center	USA	RSNA Seed Grant and the Rays of Hope charitable fund	34	6 months	9%
Pfleiderer et al. 2003[124]	MRI guidance automated gun 14G	6.4	Prospective	1	General hospital	Germany	NR	14	2 years	0%
Philpotts et al. 2003[56]	Multiple methods	4.6	Retrospective	1	General hospital	USA	NR	281	Mean: 19 months Range: 3 to 53 months for 14G Mean: 13 months Range: 1 to 24 for 11G	24%
Wong and Hisham 2003[44]	Freehand automated gun 14 or 16G	7.1	Prospective	1	General hospital	Malaysia	NR	150	Range: 6 to 13 months	0%
Apesteguia et al. 2002[112]	Stereotactic guidance vacuum-assisted 11G	7.1	Prospective	1	General hospital	Spain	NR	132	1 year	0%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Georgian-Smith et al. 2002[113]	Stereotactic guidance vacuum-assisted 11G	5.7	Retrospective	4	General hospital	USA	NR	185	Range: 6 to 12 months	21%
Jackman and Lamm 2002[132]	Multiple methods	5.4	Retrospective	1	General hospital	USA	Funded in part by Biopsys Medical	31	At least 6 months	0%
Johnson et al. 2002[102]	US guidance vacuum-assisted 11 or 8G	6.4	NR	1	General hospital	USA	Fashion Footwear of NY	101	Mean: 9.5 months	24%
Liberman et al. 2002[114]	Stereotactic guidance vacuum-assisted 11G	4.3	Retrospective	1	General cancer center	USA	NR	800	At least 1 year	29%
Meloni et al. 2002[115]	Stereotactic guidance vacuum-assisted	6.1	Retrospective	1	General hospital	Italy	NR	129	Mean: 18.7 months Range: 14 to 26 months	0%
Morris et al. 2002[116]	Stereotactic guidance vacuum-assisted 14G	6.4	Prospective	1	Dedicated breast cancer center	USA	NR	21	Median: 46 months Range: 40-54 months	10%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Pfarl et al. 2002[117]	Stereotactic guidance vacuum-assisted 11G	6.1	Retrospective	1	General hospital	Austria	NR	332	Immediate surgery	4%
Verkooijen et al. COBRA 2002[68]	Stereotactic guidance automated gun 14G	7.9	Prospective	5	General hospital	the Netherlands	Dutch National Health Insurance Fund Council	984	Immediate surgery	11%
Becker et al. 2001[69]	Stereotactic guidance automated gun 14G	5.0	Retrospective	1	General hospital	Canada	NR	232	Range: 6 to 12 months	27%
Brenner et al. 2001[70]	Stereotactic guidance automated gun 14G	6.1	Prospective	7	Cancer centers and hospitals	USA	NR	1,003	Mean: 19.3 months Range: 0 to 36 months	1%
Cangiarella et al. 2001[118]	Stereotactic guidance vacuum-assisted 11G	6.1	NR	1	General hospital	USA	NR	160	Mean: 20.5 months Range: 6 to 35 months	38%
Dahlstrom and Jain 2001[71]	Stereotactic guidance automated gun 14G	6.8	NR	1	General hospital	Australia	NR	301	Range: 2.4 to 7.5 years	0%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Lai et al. 2001[119]	Stereotactic guidance vacuum-assisted 11G	6.4	NR	1	General hospital	Canada	NR	673	Mean: 6.7 months Range: 6 to 24 months	29%
Levin et al. 2001[72]	Stereotactic guidance automated gun 14G	7.1	Prospective	1	General hospital	Canada	Physician's Services Incorporated Foundation	70	Immediate surgery	0%
Margolin et al. 2001[133]	Multiple methods	5.4	Retrospective	1	General hospital	USA	NR	1,333	Mean: 14 months Range: 6 to 24 months; missing data was collected from SEER database; at the time of accession of SEER data followup ranged from 15 to 75 months.	3%
Perez-Fuentes et al. 2001[103]	US guidance vacuum-assisted 11G	4.6	NR	1	Dedicated breast cancer center	Venezuela	NR	88	Median: 11.1 months Range: 4 to 24 months.	33%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Smith et al. 2001[57]	US guidance automated gun 14G	6.1	NR	1	General hospital	USA	NR	500	Mean: 22 months Median: 14 months Range: 12 to 60 months	21%
White et al. 2001[134]	Multiple methods	4.6	Retrospective	1	General hospital	USA	NR	1,042	Median: 29 months, at least 1 year	29%
Wunderbaldinger et al. 2001[58]	US guidance automated gun 14G	6.1	Prospective	1	General hospital	Austria	author supported by Erwin Schroedinger Auslandsstipenium of the Austrian Science Fund	45	Immediate surgery	0%
Yeow et al. 2001[59]	US guidance automated gun 14 or 16G	7.1	Prospective	1	General hospital	China	NR	98	Mean: 4 years Range: 3 to 5 years	0%
Beck et al. 2000[120]	Stereotactic guidance vacuum-assisted 11G	6.8	NR	1	General hospital	Germany	NR	594	1 year	0%
Kirwan et al. 2000[73]	Stereotactic guidance automated gun 14G	5.0	Retrospective	1	General hospital	UK	NR	72	Immediate surgery	13%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Latosinsky et al. 2000[135]	Multiple methods	5.4	Retrospective	1	General hospital	USA	NIH grant	692	Median: 17.2 months Range: 2.8 to 43 months	42%
Liberman et al. 2000[136]	Multiple methods	4.6	Retrospective	1	General cancer center	USA	NR	155	Median: 53 months Range: 24 to 69 months	32%
Makoske et al. 2000[137]	Multiple methods	5.4	Retrospective	1	General hospital	USA	NR	817	Mean: 1.7 years	30%
Ward et al. 2000[74]	Stereotactic guidance automated gun 14G	6.1	NR	1	General hospital	Canada	NR	121	Mean: 16 months Range: 4 to 36 months	7%
Welle et al. 2000[138]	Multiple methods	3.6	Retrospective	3	General hospital	USA	NR	225	Range: 6 to 24 months	20%
Helbich et al. 1999[150]	Multiple methods	6.1	Prospective	1	General hospital	Austria	Ludwig-Boltzmann Institute for Radiologic Tumor Research; one author was supported by a grant from the Max Kade Foundation	44	Immediate surgery	0%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Jackman et al. 1999[75]	Stereotactic guidance automated gun 14G	5.0	Retrospective	1	General hospital	USA	NR	483	Median: 55 months	1%
Meyer et al. 1999[139]	Multiple methods	4.6	Retrospective	1	General hospital	USA	NR	1,836	At least 1 year	25%
Puglisi et al. 1999[125]	Perforated compression grid automated gun 14G	5.4	Retrospective	1	General hospital	Italy	NR	106	At least 6 months	1%
Soo et al. 1999[76]	Multiple methods	5.0	Retrospective	1	General hospital	USA	NR	116	Mean: 16 months Range: 5 to 31 months	19%
Caruso et al. 1998[140]	Multiple methods	6.8	Prospective	1	General hospital	Italy	NR	92	Immediate surgery	13%
Doyle et al. 1998[77]	Stereotactic guidance automated gun 14G	5.0	Retrospective	1	Dedicated breast cancer center	New Zealand	NR	151	Range: 6 to 36 months	11%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Fuhrman et al. 1998[141]	Multiple methods	4.6	Retrospective	1	General hospital	USA	NR	1,440	At least 6 months	18%
Heywang-Kobrunner et al. 1998[121]	Stereotactic guidance vacuum-assisted 11 or 14G	6.1	NR	1	General hospital	Germany	NR	261	6 months	31%
Ioffe et al. 1998[142]	Multiple methods	6.1	NR	1	General hospital	USA	NR	224	Range: 6 to 12 months	14%
Liberman et al. 1998[60]	US guidance automated gun 14G	6.4	NR	1	General cancer center	USA	NR	151	Median: 20 months Range: 6 to 48 months	23%
Schulz-Wendtland et al. 1998[61]	US guidance automated gun 14G	6.8	NR	1	General hospital	Germany	NR	307	2 years	0%
Vega-Bolivar et al. 1998[78]	Stereotactic guidance Surecut 15G	4.6	Retrospective	1	General hospital	Spain	NR	182	Mean: 27 months Range: 6 to 47 months	6%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Whitman et al. 1998[79]	Stereotactic guidance automated gun 16G	5.4	Retrospective	2	General hospital	USA	NR	12	Immediate surgery	0%
Zannis and Aliano 1998[80]	Multiple methods	5.7	Retrospective	1	Ambulatory surgical center	USA	NR	424	At least 6 months	31%
Bauer et al. 1997[81]	Stereotactic guidance automated gun 14G	5.7	Retrospective	NR	NR	USA	NR	799	Mean: 9 months	0%
Britton et al. 1997[143]	Multiple methods	6.8	NR	1	General hospital	UK	NR	202	Mean: 20.1 months Range: 5.3 to 30.8 months	2%
Helbich et al. 1997[144]	Multiple methods	7.1	Prospective	1	General hospital	Austria	NR	210	Immediate surgery	0%
Khattar et al. 1997[62]	US guidance automated gun	6.4	Prospective	1	General hospital	Denmark	NR	106	Immediate surgery	43%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Liberman et al. 1997[82]	Stereotactic guidance automated gun 14G	4.3	Retrospective	1	General cancer center	USA	NR	442	Median: 18 months Range: 6 to 46 months	34%
Pitre et al. 1997[83]	Stereotactic guidance automated gun	5.4	Retrospective	1	General hospital	USA	NR	128	1 year	8%
Stolier et al. 1997[145]	Multiple methods	5.4	Retrospective	1	General hospital	USA	NR	244	Mean: 12.8 months Range: 6 to 39 months	NR
Sutton, et al. 1997[84]	Stereotactic guidance automated gun 14G	3.6	Retrospective	1	Screening clinic	Australia	NR	206	1 year	32%
Walker et al. 1997[85]	Stereotactic guidance automated gun 14G	6.8	NR	1	General hospital	UK	NR	200	Range: 6 to 36 months	10%
Frazee et al. 1996[86]	Stereotactic guidance automated gun	7.1	Prospective	1	General hospital	USA	NR	103	At least 6 months	0%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Fuhrman et al. 1996[87]	Stereotactic guidance automated gun 14G	5.4	NR	1	General hospital	USA	NR	451	1 year	22%
Head and Haynes 1996[88]	Stereotactic guidance automated gun 18G	6.4	Prospective	1	Dedicated breast cancer center	USA	NR	115	2 years	8%
Mainiero et al. 1996[89]	Stereotactic guidance automated gun 14G	6.1	Retrospective	1	General hospital	USA	NR	138	At least 6 months	14%
Meyer et al. 1996[90]	Stereotactic guidance automated gun 14G	5.4	NR	1	General hospital	USA	NR	388	1 year	30%
Nguyen et al. 1996[146]	Multiple methods	6.4	NR	1	General hospital	USA	American Cancer Society, UCLA Jonsson Comprehensive Cancer Center, and the Stein-Oppenheim Foundation	431	At least 6 months	10%
Pettine et al. 1996[91]	Stereotactic guidance automated gun 14G	6.1	Retrospective	1	General hospital	USA	NR	25	6 month repeat mammo-graphy for benign	0%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Rosenblatt et al. 1996[92]	Stereotactic guidance automated gun 14G	4.6	Retrospective	1	General hospital	USA	NR	25	1 year	16%
Scopa et al. 1996[45]	Freehand TruCut	6.8	NR	1	General hospital	Greece	NR	120	Immediate surgery	0%
Cross et al. 1995[93]	Stereotactic guidance automated gun 14G	5.0	NR	1	Dedicated breast cancer center	USA	NR	250	1 year	12%
Doyle et al. 1995[147]	Multiple methods	6.4	Prospective	1	General Hospital	USA	NR	150	Range: 6 to 24 months	3%
Hamed et al. 1995[151]	Freehand Biopty-cut	6.1	Prospective	1	General hospital	UK	NR	122	Immediate surgery	0%
Burbank et al. 1994[148]	Multiple methods	5.7	NR	1	General hospital	USA	NR	105	At least 6 months	0%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Gisvold et al. 1994[94]	Stereotactic guidance automated gun 14G	6.4	Prospective	1	General hospital	USA	NR	160	Immediate surgery	0%
Parker et al. 1994[149]	Multiple methods	3.9	Retrospective	20	Various hospitals, breast care centers, clinics	USA	NR	6,152	At least 6 months	39%
Smyth and Cederbom 1994[95]	Stereotactic guidance automated gun 14G	4.6	NR	1	General hospital	USA	NR	58	Immediate surgery	0%
Elvecrog et al. 1993[96]	Stereotactic guidance automated gun 14G	7.9	Prospective	1	General hospital	USA	NR	100	Immediate surgery	0%
Parker et al. 1993[63]	US guidance automated gun 14G	6.8	NR	1	Specialized imaging center	USA	NR	181	Range: 12 to 36 months	0%
McMahon et al. 1992[46]	Multiple methods	6.8	Prospective	1	General hospital	UK	NR	151	Median: 11 months Range: 1 to 24 months	0%

Table 5. Studies addressing Key Questions 1 and 2 (continued)

Study	Type(s) Core Biopsy	Quality score	Type of Study	Number of Centers	Care Setting	Country Conducted in	Funded by	Number of Lesions Enrolled	Followup	% Attrition at Longest Followup
Barreto et al. 1991[47]	Freehand automated gun 18G	6.8	NR	1	General hospital	UK	NR	107	Immediate surgery	0%
Cusick et al. 1990[48]	Freehand	6.1	NR	1	General hospital	USA	NR	96	Immediate surgery	0%
Parker et al. 1990[97]	Stereotactic guidance automated gun	5.7	NR	1	General hospital	USA	NR	103	Immediate surgery	0%

NR = Not Reported
USA = United States of America
UK = United Kingdom

Table 6. Summary of accuracy by type of biopsy procedure

Type of biopsy	N studies	N lesions	Prevalence of malignancy	Sensitivity (95% CI)	Negative likelihood ratio (95% CI)	Atypia underestimation rate	DCIS underestimation rate
Freehand automated gun	5	610	68.7%	85.8% (75.8 to 92.1%)	0.143 (0.082 to 0.250)	Not reported	Not reported
US guidance automated gun	16	7,124	53.9%	97.7% (97.2% to 98.2%)	0.030 (0.022 to 0.040)	0.292 (0.234 to 0.359)	0.355 (0.271 to 0.450)
Stereotactic guidance, automated gun	33	7,153	37.1%	97.8% (95.8% to 98.9%)	0.022 (0.012 to 0.043)	0.435 (0.357 to 0.517)	0.244 (0.180 to 0.321)
MRI guidance, automated gun	1	14	42.8%	83.3% (43.5% to 96.5%)	0.23 (0.05 to 0.95)	100% (1/1)	NR
Perforated compression grid automated gun	1	100	33%	91.4% (77.5% to 96.9%)	0.09 (0.03 to 0.26)	0.25 (1 out of 4)	0.286 (2 out of 7)
US guidance vacuum-assisted	7	507	15%	96.5% (81.2 to 99.4%)	0.036 (0.006 to 0.212)	None reported	Only one occurrence reported
Stereotactic guidance, vacuum-assisted	21	6,360	32.6%	99.2 % (97.9% to 99.7%)	0.009 (0.003 to 0.023)	0.217 (0.177 to 0.264)	0.130 (0.111 to 0.151)

NR = Not Reported

Table 7. Summary of the impact of factors on accuracy

Factors	N Studies Reported Data on the Impact of the Factor on Accuracy	Conclusion
Patient age	1	Insufficient data
Breast density	1	Insufficient data
Patient co-morbidities	0	Insufficient data
Palpable vs. non-palpable	2	Insufficient data
Microcalcifications vs. masses	4	Inconsistent findings
Distortions vs. masses	1	Insufficient data
Size of lesion	2	Insufficient data
Location of lesion	1	Insufficient data
Number of cores	3	Inconsistent findings
Patient position	1	Insufficient data
Reference standard	68	Meta-regression found no impact
Use of vacuum	78	Vacuum-assistance improved accuracy
Use of image guidance	78	Image guidance improved accuracy; stereotactic guidance was more accurate than US guidance
Needle size	33	Meta-regression found no impact
Experience of operator	2	Insufficient data
Training of operator	0	Insufficient data
Facility location	68	Meta-regression found no impact
Facility type	33	Meta-regression found no impact

Question 2. In women with a palpable or non-palpable breast abnormality, what are the harms associated with core-needle breast biopsy compared to the open biopsy technique in the diagnosis of breast cancer?

The evidence for Key Question 1, 107 studies of overall low quality, was used to address Key Question 2. Fifty of the 107 included studies did not report any harms (see Appendix F); whether this was because no harms occurred is unclear. Five studies only reported that no severe complications or harms occurred. Tonegutti and Giradi reported that (unspecified) complications only occurred during the first year of performing stereotactically-guided vacuum-assisted biopsies.[104]

Very few of the included studies reported information about complications occurring in association with open surgical biopsy procedures. We consulted a narrative review published in 2007 to obtain further information about complications of open surgical biopsy procedures. In this review, Vitug and Newman report that 2 to 10% of breast surgeries are complicated by hematoma formation, and that 3.8% are complicated by infections.[152] Rissanen et al. reviewed a series of 425 wire-localized open biopsy procedures and reported that 10.2% were complicated by vasovagal reactions.[153]

Use of Pain Medications

Four studies reported information on the use of pain medications.[80,101,102,124] These studies reported that 100% of patients were sent home with narcotics after an open biopsy procedure, and only one patient (0.17%) required narcotics after a core-needle procedure.[102] Twenty (3.5%) patients were reported to have required acetaminophen after a core-needle procedure.[101] Note that being sent home with a medication may not necessarily mean the patients required or used the medication.

Bruising, Bleeding, and Hematomas

Twenty-four studies of 17,585 core-needle biopsy procedures reported that only 0.085% were complicated by hematomas that required treatment.[56,57,59,66,81,90,94,96,100-102,104,106,109,112-115,120,138,139,143,146,149] These studies reported that 3.85% of vacuum-assisted procedures were complicated by hematoma formation, and only 0.14% of vacuum-assisted procedures were complicated by hematomas that required treatment. In comparison, only 0.24% of non-vacuum-assisted procedures were reported to be complicated by hematoma formation, and only 0.035% of non-vacuum-assisted procedures were complicated by hematomas that required treatment. Due to inconsistency in reporting, these percentages should be used with caution; however, vacuum-assisted procedures do appear to have a higher rate of hematoma formation than other core-needle biopsy methods, although overall, hematomas rarely complicate core-needle procedures.

Twenty-four studies of 8,474 core-needle biopsy procedures reported that 1.4% were complicated by bleeding, but only 0.3% were complicated by bleeding that required treatment.[44,46,53,56,69,80,85,97,98,100,102-104,109,112-115,121,130-132,135,138] Of the vacuum-assisted procedures, 0.94% were reported to be complicated by bleeding, but only 0.34% of vacuum-assisted procedures were complicated by bleeding that required treatment or termination of the procedure. In comparison, 0.55% of non-vacuum-assisted procedures were reported to be

complicated by bleeding, and only 0.20% of non-vacuum-assisted procedures were reported to be complicated by bleeding that required treatment. Due to inconsistency in reporting these percentages should be viewed with caution; however, vacuum-assisted procedures do appear to be complicated by bleeding more often than non-vacuum-assisted procedures, although bleeding is a rare complication of core-needle procedures.

Nine studies reported that bruising occurred after core-needle biopsy procedures.[46,57,59,85,90,99,101,108,141] Three of the nine reported that bruising was a common event,[46,85,141] two reported that approximately 50% of patients had bruising,[90,101] and four studies reported that 45 out of 976 patients (4.6%) had severe bruising.[57,59,99,108] These nine studies used a variety of core-needle procedures.

Infections

March et al. reported that 2.1% of open biopsy procedures were complicated by the development of an abscess, but zero abscesses complicated 234 ultrasound-guided vacuum-assisted core-needle procedures.[101] Tonegutti and Girardi reported that one abscess that required surgical treatment occurred in a series of 268 stereotactically-guided vacuum-assisted procedures.[104] None of the other studies reported the occurrence of abscesses.

Twenty studies of 16,407 core-needle procedures reported that only 0.15% of the procedures were complicated by infections.[44,53,57,59,66,77,81,85,93,94,97,98,102,106,108,109,133,135,139,149] Zannis and Aliano reported that 6.3% of open surgical biopsies were complicated by infections.[80]

Pain

Three vacuum-assisted biopsy procedures (out of over 6000 performed) were reported to have been terminated after patients complained of severe pain.[76,108,114] No other types of biopsy procedures were reported to have been terminated due to patient complaints of pain. Seventeen studies of a wide variety of biopsy methods reported information about patient pain during the procedure, and overall only 1.7% of patients were reported to have experienced severe pain.[44,46,76,84-86,93,94,96,100,101,108,112,114,121,146]

Frazee et al. reported the mean pain score (10-point VAS scale) was 2.5 for open biopsy procedures and 2.8 for stereotactically-guided automated gun core-needle biopsies (the difference was not statistically significant).[86]

Wong and Hisham reported no difference in the amount of pain experienced by patients undergoing a 14G core-needle procedure vs. a 16G core-needle procedure.[44] McMahon et al. reported that patients undergoing 18G core-needle procedures had significantly less pain than patients undergoing 14G core-needle procedures, but there was no significant difference in pain between 14G and 16G procedures.[46]

Vasovagal Reactions

Twenty-two studies of 7,526 core-needle procedures reported that 1% were complicated by vasovagal reactions (fainting or near-fainting).[58,66,69,72,77-79,85,94,97,98,104,109,113-115,125,131,138,139,143,144] More than 40% of the vasovagal reactions occurred in patients who were reported to have been positioned sitting upright for the biopsy procedure (many of the studies did not report patient position so the other 60% of vasovagal reactions could have occurred in patients positioned in a variety of positions, or could have occurred primarily in seated patients).

Kirshenbaum et al. commented that the majority of vasovagal reactions occurred when inexperienced operators performed the biopsy procedures.[131]

Time to Recovery

One study, Frazee et al., reported information about time to recovery, measured by asking patients how long it had taken for them to return to their normal activities after the biopsy procedure. This study reported that the average time of recovery was 3.5 days for open biopsy procedures and 1.5 days for stereotactically-guided automated gun core-needle biopsy procedures.[86]

Impact of Biopsy Procedure on Usual Activities

One study, March et al., reported that ultrasound-guided vacuum-assisted procedures did not impact the usual activities of 47% of the women at all.[101]

Impact of Biopsy Procedure on Subsequent Mammographic Procedures

Three studies reported information about the impact of core-needle biopsies on subsequent mammographic examinations.[109,120,121] All three studies performed stereotactic-guided vacuum-assisted core-needle procedures. These three studies enrolled 3,748 patients of whom 3,345 (89.2%) were reported to have no mammographically visible scarring after the biopsy procedures. Only seven of the patients (0.19%) were reported to have scars that were potentially diagnostically confusing on subsequent mammographic procedures.

Miscellaneous Reported Harms

Four studies of 2,600 patients reported that four cases of pneumothorax, none of which required treatment, had occurred.[104,109,113,120] None of these four studies used the same method of performing the core-needle biopsies.

Two studies reported that one patient per study (out of 3,487 patients) had suffered a seizure during a stereotactic-guided vacuum-assisted procedure.[109,120]

One study of 268 patients undergoing stereotactic-guided vacuum-assisted biopsies reported that three patients developed acute inflammation at the biopsy site after the procedure.[104]

One study of 185 stereotactic-guided vacuum-assisted procedures reported that one patient vomited during the procedure.[113]

Dissemination of Cancerous Cells During the Biopsy Procedure

To address this possible harm of a breast biopsy we did not use formal inclusion criteria; any clinical study that addressed the topic was included for discussion. Full details of the studies are shown in Appendix E. The results of the studies are summarized in Table 8.

We identified ten studies that used histopathology to demonstrate dissemination of cancerous cells by core-needle biopsy procedures.[154-163] The percentage of needle tracks reported to contain displaced cancerous cells ranged from 0% to 65%. Diaz et al. demonstrated that the time elapsed between core-needle biopsy and examination of the needle track strongly influenced the findings, with fewer and fewer displaced cancerous cells observed the longer the interval, suggesting that the majority of displaced cancerous cells die off over time.[154] However, we also identified six case reports of patients developing tumor recurrences at the site of prior core-needle biopsies, indicating that not all displaced cancerous cells are non-viable.[155,161,164] Three of these six women were reported not to have received radiation therapy for the primary tumor; for the other three women it was not reported whether or not they had received radiation therapy.

The risk of tumor recurrence following biopsy was explored by four retrospective studies of 1,879 women.[165-168] Three of these four studies reported that women who did not have a pre-operative needle biopsy had a higher rate of tumor recurrence than women who did receive a pre-operative needle biopsy;[165-167] the fourth study reported the opposite.[168] The majority of the women in these four studies were treated with breast-conserving surgery and radiation therapy.

The risk of seeding the lymph nodes with cancerous cells by biopsy procedures was examined in three retrospective studies of 3,103 patients.[169-171] Two of the three studies reported that the method of biopsy did not affect the rate of positive sentinel lymph nodes;[169,171] the third study reported that the rate of metastases to the sentinel lymph node was higher in women who underwent some form of pre-operative biopsy.[170]

In 2006 Bleiweiss et al. reported 25 cases of false-positive sentinel lymph nodes.[172] All 25 cases appeared to be caused by displacement of benign epithelial cells during a prior biopsy procedure. Twelve of the false-positive cases had undergone core-needle biopsy prior to the sentinel lymph procedure, 12 had undergone wire-localization open biopsy procedures, and one had undergone a fine-needle aspiration procedure. Although these cases are not, strictly speaking, cases of seeding lymph nodes with cancerous cells, this study is of clinical importance. False-positive sentinel lymph node procedures are likely to lead to over-treatment of patients, thus causing harm. These false-positive cases had stained positively for the presence of cytokeratins due to the presence of benign breast epithelial cells in the lymph nodes. Fifteen of the false-positives occurred in women with pure DCIS, and the remainder had DCIS plus invasive carcinoma. Twenty-two of the 25 cases had intraductal papilloma, (a not uncommon breast lesion) at the biopsy site and showed signs of displacement of benign cells at the biopsy site. The authors of this series of case reports suggest using caution when interpreting sentinel lymph node histopathology in cases where intraductal papilloma was noted during the initial biopsy procedure.

Table 8. Dissemination of cancerous cells during biopsy procedures

Type of study	Number of studies	Number of patients	Summary of findings
Histopathological demonstration of dissemination of cells	3 case reports[155-157] 1 retrospective study[163] 6 prospective studies[154,158-162]	786	The percentage of needle tracks reported to contain displaced cancerous cells ranged from 0% to 65%. Factors reported to increase the risk of finding displaced cancerous cells include: duration of the biopsy procedure,[158] multiple passes of the needle,[159] and a short interval between core-needle procedure and surgical excision.[154] Factors reported to decrease the risk of finding displaced cancerous cells include: diagnosis of invasive lobular carcinoma,[159] and use of vacuum-assisted core-needle biopsy.[154]
Tumor recurrence at the biopsy site	3 case reports[155,161,164]	6	6 cases of tumor recurrence at the biopsy site were presented. All were treated with skin-sparing mastectomy following core-needle biopsy , and three were reported to have not received radiation treatment.[155,161] It was not reported whether the other 3 cases received radiation treatment.[164]
Risk of tumor recurrence following biopsy	4 retrospective studies[165-168]	1,879	Three of the four studies reported that women treated with open excisional biopsies had a higher rate of tumor recurrence than women who received pre-operative core-needle biopsies;[165-167] the fourth study reported opposite findings.[168] The majority of women in all four studies were treated with breast-conserving surgery and radiation therapy.
Risk of metastasis to the lymph nodes following biopsy	3 retrospective studies[169-171]	3,103	Two studies reported that the method of biopsy did not correlate with the rate of metastases to the sentinel lymph nodes;[169,171] one study reported that the rate of metastases to the sentinel lymph nodes was higher in women who underwent some type of pre-operative needle biopsy than in women who underwent open excisional biopsy.[170]

Table 9. Summary of harms complicating core-needle biopsies

Harms	N Studies Reported	N Lesions	N Occurrences	% Affected
Did not report	50	28,280	NR	NR
Reported no complications occurred	5	3,954	0	0%
Negative impact on quality of life	0	0	NR	NR
Patients dissatisfied with the procedure	2	328	2	0.61%
Hematomas requiring treatment	24	17,585	15	0.09%
Bleeding, severe	24	8,474	61	0.72%
Infections	20	16,407	24	0.15%
Pneumothorax	4	2,600	4	0.15%
Usual activities significantly affected by the biopsy procedure	1	34	4	11.80%
Time to recovery	1	103	1.5 days on average	NA
Bruising	9	3,256	Reported to be "common"	NR
Required pain medications	4	573	21	3.70%
Diagnostically confusing scars subsequent to the procedure	3	3,748	7	0.18%
Vasovagal reactions	22	7,631	77	1.00%
Severe pain during the biopsy procedure	17	3,128	52	1.70%

NR = Not Reported
NA = Not Applicable

Table 10. Summary of the impact of factors on harms

Factors	N Studies Reported Data on the Impact of the Factor on Harms	Conclusion
Patient age	0	Insufficient data
Breast density	0	Insufficient data
Patient co-morbidities	0	Insufficient data
Palpable vs. non-palpable	0	Insufficient data
Microcalcifications vs. masses	0	Insufficient data
Distortions vs. masses	0	Insufficient data
Size of lesion	0	Insufficient data
Location of lesion	0	Insufficient data
Number of cores	0	Insufficient data
Patient position	22	Vasovagal reactions occur more often in patients seated upright
Reference standard	0	Insufficient data
Use of vacuum	24	Use of vacuum increased the percentage of procedures complicated by severe bleeding and hematoma formation
Use of image guidance	0	Insufficient data
Needle size	1	Insufficient data
Experience of operator	0	Insufficient data
Training of operator	0	Insufficient data
Facility location	0	Insufficient data
Facility type	0	Insufficient data

Question 3. How do open biopsy and various core-needle techniques differ in terms of patient preference, availability, costs, availability of qualified pathologist interpretations, and other factors that may influence choice of a particular technique?

We did not use formal inclusion criteria to select literature that addressed Key Question 3 due to the nature of the question. Data addressing this question were collected and are shown in Appendix E. The data are summarized in Table 13, Table 14, and Table 15, and are discussed outcome-by-outcome below. Economic factors that may influence the choice of a particular technique are discussed first, followed by factors highly important to patients, followed by other factors such as availability of equipment. Because of the nature of the question and the sources of information used to address it, we did not draw many formal evidence-based conclusions for this question, nor, in most cases, did we attempt to rate the quality of the studies or grade the strength of the evidence.

Relative Costs

Articles identified by our searches that analyzed the costs of open and various core-needle biopsy techniques in the U.S. health care system within the last five years (published in or after 2004) are summarized in Table 11. The relative costs of open surgical biopsy and various core-needle biopsy techniques have been evaluated by six studies. Some of the studies developed models, while others prospectively followed a patient population. When evaluating the costs of these techniques and procedures, the studies have reviewed factors such as the initial purchase price of the devices used, the costs of staffing, the costs of processing and analyzing the biopsy samples, the patient volume where the device will be utilized, if the device is used as a complementary procedure, and what mammography results determine the use of a core-needle biopsy technique.

According to the literature reviewed, the costs of open surgical biopsy are substantially higher than core-needle techniques. A study by Hatmaker et al. in 2007 found that the average total cost of an open surgical biopsy performed in the operating room was $4,368 (presumably 2003-2005 U.S. dollars) with a median cost of $3,479 and the average total cost of image-guided core-needle biopsy was $1,267 with a median cost of $1,239.[173]

The results of a mammogram help surgeons and radiologists decide which core-needle technique, if any, would be beneficial and ultimately cost-effective for the patient and facility. Soo et al. used a decision analysis model to compare the costs of a 14-gauge core-needle biopsy to a 14-gauge and 11-gauge vacuum-assisted biopsy for noncalcified lesions. They found that the 14-gauge CNB is less costly for noncalcified lesions, which is not surprising since vacuum-assisted equipment is more expensive.[174] Golub et al. prepared a cost-minimization model and found that image-guided core-needle biopsy was favored (cost the least) over open biopsy for low suspicion lesions, calcifications, and masses, primarily due to savings from reducing the overall number of surgeries performed.[175]

The cost to purchase a core-needle biopsy system is another factor of interest to facilities. In an article published in 2003, Kirshenbaum et al. reported that the average list price for a breast imaging center to make an existing mammography unit biopsy ready (i.e add-on unit) was $90,000 and the average list price for a dedicated prone biopsy table was $226,000.[131] Current quoted prices (not list prices) are about $170,000 (2008 U.S. dollars) for a dedicated table (which

also requires a large dedicated room) and about $100,000 for an add-on unit.[176] Unlike a dedicated prone biopsy table, a mammography unit with an add-on device can be used for general mammography purposes when not being used for a biopsy procedure. However, add-on units have limitations, including limited access angles, limited ability to restrict patient movement, and less patient comfort than dedicated units.[176]

Ultrasound-guided core-needle biopsies do not require special equipment and can be performed with a standard multi-purpose US device. Vacuum-assisted core-needle devices currently cost around $37,000 (2008 U.S. dollars) to purchase a console, and require $270 single-use probes.[176] MRI-guidance is the most expensive method of performing core-needle biopsies, requiring expensive specialized equipment as well as access to an MRI facility.[176]

Spared Surgical Procedures

We identified 31 studies that reported information on how the use of core-needle biopsy spares women additional surgical procedures (see Table 12; also see Appendix E for further details). Women who undergo open biopsy with positive findings often undergo additional surgical procedures to ensure the entire lesion has been removed and to sample the lymph nodes. Women who undergo a core-needle biopsy procedure with positive findings may be able to undergo a single surgical procedure that simultaneously confirms the diagnosis and removes the entire lesion, and samples the lymph nodes if necessary, thus being spared additional surgical procedures. Women who undergo a core-needle biopsy with negative findings may be able to avoid surgical procedures altogether. Liberman et al. reported that, before the introduction of core-needle biopsy, 29% of women diagnosed with cancer had only one surgical procedure, but after the introduction of core-needle biopsy that number rose to 84%.[177] The studies consistently reported that approximately 75% of women who underwent a core-needle biopsy procedure were spared further procedures, with a mean of approximately 1.2 procedures per woman compared to 1.5 to 2.0 procedures per woman who was initially evaluated with open surgical biopsy.

Seven of the studies reported information about the percentage of women who, after being diagnosed with breast cancer by either core-needle or open biopsy, were able to be treated for their cancer with a single surgical procedure. We combined the data reported by these studies in a meta-analysis. The data were consistent ($I^2 = 2.2\%$). The summary odds ratio is 13.7 (95% CI: 5.6 to 34.6), an extremely large magnitude of effect. We felt that the strength of association between the type of biopsy and being able to treat the breast cancer with only one surgical procedure was strong enough to support an evidence-based conclusion. Although the internal validity (study quality) was low, the evidence was robust, consistent, and had an extremely large magnitude of effect. We therefore graded the strength of evidence supporting the conclusion as Moderate.

Procedure Preference

We identified 20 studies that reported data on patient preferences (see Table 12; also see Appendix E for further details). Ten of the 20 studied vacuum-assisted methods. The majority of the studies did not directly compare different biopsy procedures and instead reported information such as that the patients tolerated the procedure well or would recommend it to others in the future. One study reported that patients preferred the decubitus position to the prone position.[138] Two studies reported that vacuum-assisted procedures were more comfortable than other types of core-needle biopsies.[178,179] Two authors reported that patients lost less time to core-needle procedures than to open procedures.[100,180] The majority of the studies concluded that core-needle

biopsies were preferable to open biopsies, but one study reported that a survey of patients found that 90% were satisfied with their open surgical biopsy compared to only 80% satisfied with a vacuum-assisted core-needle biopsy.[181]

Cosmetic Results

We identified ten studies that reported information on cosmetic results (see Table 12; also see Appendix E for further details). The studies all used vacuum-assisted core-needle biopsy methods. The authors of the studies reported information on how patients felt about the cosmetic results post-procedure. Overall, patients were reported to have been satisfied with the cosmetic results. Only one of the ten studies, Chun et al., compared a group of patients undergoing core-needle biopsy to a group of patients undergoing open biopsy.[181] Chun et al. compared cosmetic results of patients undergoing wire-localized open biopsy to patients undergoing vacuum-assisted 11-gauge core-needle biopsy two years post-procedure. Ninety-five percent of the core-needle biopsy group and only 25% of the open biopsy group were very satisfied with the appearance of their breast. None of the core-needle biopsy group said the cosmetic results were unacceptable compared to 20% of the open biopsy group who found the results unacceptable.

Although all of the studies reporting on cosmetic results used vacuum-assisted methods, it is likely the results apply to most forms of core-needle biopsy. Regardless of the needle gauge or method used, the actual incision cut in the skin for core-needle procedures is always approximately ¼" long.[176]

Physician Experience

We identified ten studies that reported information concerning physician experience (see Table 12; for further details see Appendix E). Authors of some of the studies commented that certain devices were easier for inexperienced physicians to use. In general, however, the authors of the studies concluded that greater experience with particular devices improved the accuracy of the biopsy procedures, shortened procedure duration times, and led to a decrease in the number of open biopsies that were performed.

Availability of a Qualified Pathologist

We identified two studies that discussed pathologist qualifications and availability (see Table 12; for further details see Appendix E). One reported that whether a specimen was read by a local or central pathologist made little difference because concordance between readings was 96.1% ($\kappa = 0.90$) for core needle biopsy and 92.6% ($\kappa = 0.93$) for open surgical biopsy. However, there was greater disagreement with respect to ADH and ALH for both biopsy types, with underestimation of the lesion by local pathologists in comparison to the central pathology laboratory (for CNB, ADH agreement 63% and ALH agreement 53%; for open, ADH agreement 45% and ALH agreement 73%).[182] The authors of the other study speculated that lack of an experienced pathologist was the cause of the low accuracy of the core-needle biopsies performed during the course of their study.[183]

Availability of Equipment

We identified three studies that talked about the impact of equipment availability (see Table 12; for further details see Appendix E). One reported that vacuum-assisted devices were more commonly available in the U.S. than in Europe.[184] One reported that wait times for access

to core-needle procedures were significantly shorter than wait times for access to open surgical procedures.[185] The authors of the third study reported that wait times for access to a dedicated prone biopsy table were longer than wait times for other types of core-needle biopsy.[186]

Resource Usage

We identified two studies that talked about resource usage (see Table 12; for further details see Appendix E). The authors of one study reported that vacuum-assisted procedures required more physician and room time than free-hand ultrasound-guided procedures.[187] The other study reported that dedicated prone tables use four times as much space as non-prone units.[188]

Procedure Duration Time

We identified 40 studies that reported information about the duration of different biopsy procedures (see Table 12; for further details see Appendix E). The studies reported a wide range of times, from 10 minutes to 128 minutes. The wide range of times may be in part due to different definitions of when exactly the procedure was defined as starting and ending: for example, does the procedure start when the patient enters the room? When the incision is made? Does it end when the sample is collected or when the patient is released to go home? In general, study authors did not define what exactly they meant by procedure duration time.

The reported mean or median time to perform core-needle biopsies under ultrasound guidance ranged from 10 to 60 minutes; the mean or median time to perform core-needle biopsies under stereotactic guidance ranged from 19 to 70 minutes; and the mean or median time to perform core-needle biopsies under MRI guidance ranged from 31 to 70 minutes. Vacuum-assisted core-needle biopsies were reported to have a mean or median duration of 10 to 70 minutes. Open surgical biopsies were generally reported to have longer duration times than core-needle procedures, but only two studies reported estimated duration times of open biopsy—40 to 45 minutes.[51,189]

Wait Time for Test Results

We identified two studies that reported mean or median times to get a diagnosis following a breast biopsy (see Table 12; for further details see Appendix E). The authors reported that wait times after a core-needle procedure were 7 to 10 days shorter than after an open excisional biopsy.[183,185]

Table 11. Economic considerations

Reference	Source of Cost Data	Methods or Models of Analysis	Primary Conclusions
Hatmaker et al. 2006[173]	The Massachusetts Utilization Multiprogramming System and the Decision Support System software packages were used to track costs of procedures, by Current Procedure Terminology (CPT) code and date of service.	Data were analyzed and described using the R statistical computing environment. Costs for all service related to each procedure were linked through billing procedures by the date of service and classified as related to radiology costs, to pathology or laboratory costs, or to procedural costs	"The average total cost to evaluate a patient with a breast mass or mammographic abnormality through an OSB in the operating room was $4,368 (SD: $2,586) with a median cost of $3,479. The average total cost for a CNB was $1,267 (SD: $536) with a median cost of $1,239. For VA hospitals with available resources, the option of CNB is a cost-effective and more preferable alternative to OSB." (US currency year not specified; data collected between 2003-2005)
Orel et al. 2006[190]	NR	NR	"The total Medicare allowance for one MR-guided vacuum-assisted CNB procedure is approximately $500." (presumed to be 2005 US dollars) "Additional investigation is needed to develop more cost-efficient systems. In addition, the cost of the needles will probably decrease as the use of them increases"
Shin et al. 2006[191]	NR	NR	"If the surgeon chooses to perform a diagnostic core biopsy and then excise the lesion for definitive treatment, the overall cost would be between $12,000 and $15,000, depending on the initial modality used for biopsy. Extrapolating this to our small pilot study of 156 patients, the observation arm would cost $619,000 for ultrasound-guided CNB and $1,028,820 for stereotactic-guided CNB. OSB for diagnosis and treatment with routine screening follow-up would cost $1,454,544 at our institution." The costs appear to be charges ("costs billed at our institution). Currency year not specified but the data were collected between 2000 – 2003, and the study was presented in 2005.)
Soo et al. 2005[174]	Cost & probability variables were estimated from the authors' institution over a three-year period. Ratios were used representing the relative dollar values of the estimated costs	Decision Analysis Model was used to compare costs of 14-gauge CNB to 14-gauge and 11-gauge vacuum-assisted CNB for stereotactic biopsy of noncalcified breast lesions	The 14-G vacuum-assisted CNB was 1.19 times as expensive as the multipass automated gun CNB method, and the 11-G vacuum-assisted CNB was 1.22 times as expensive as the multipass automated gun CNB. The 14-G CNB is less costly for stereotactic biopsy of non-calcified lesions over a wide range of cost estimates

Table 11. Economics considerations (continued)

Reference	Source of Cost Data	Methods or Models of Analysis	Primary Conclusions
Golub et al. 2004[175]	Patient billing records at the Lynn Sage Breast Center	A decision analytic model of the outcomes of all biopsy patients seen at the Lynn Sage Breast Center during a 2 year period was constructed. Costs were analyzed by considering only patients receiving breast-conserving surgery (lumpectomy alone), and subgroup based on degree of suspicion and on radiographic abnormality type. The sum of the mean costs determined from the patient billing records was used as the baseline outcome measures in the decision tree. Costs were measured from a societal perspective. Only direct costs related to inpatient care were considered, and they included CNB, OSB, lumpectomy with or without re-excision, lumpectomy with or without lymph node dissection, mastectomy with or without lymph node dissection, and lymph node dissection alone. Costs were derived by application of the institution's cost-to-charge multiplier	"The total cost of diagnosis and surgical treatment was $1,849 for CNB versus $2,775 for OSB. When the probabilities were biased to favor OSB, the cost was $2,297 for CNB and $2,458 for OSB. CNB was favored for low suspicion lesions, calcifications, and masses. OSB was favored for high suspicion lesions and architectural distortion. Total costs were $926 less for the CNB group. CNB can be cost-saving compared with OSB, particularly when mammographic abnormality is classified as low suspicion or consists of calcifications or masses." (Currency year not specified, but costs were in U.S. dollars and data were collected in 1996-1998.)
Kirshenbaum et al. 2003[131]	NR	NR	"A breast imaging center need spend only approximately $90,000 (average list price of add-on device) to make an existing mammography unit biopsy-ready. For a dedicated prone biopsy table, a center would need to spend $226,000 (average list price). If one includes the additional cost of purchasing a mammography machine (average $80,000) that might be required because the add-on unit is incompatible with the existing machine, the cost differential is substantially reduced. When not being used for biopsies, add-on units can be used for general screening and diagnostic work, whereas prone units can only be used for biopsies." (U.S. Currency year not specified; manuscript submitted in 2002)

Table 12. Key Question 3: other outcomes

Outcome	Number of Studies	Number of Patients	Summary of Findings
Cosmetic results	5 prospective studies[101,103,192-194] and 5 retrospective studies[108,120,181,195,196]	4,732	In eight of the ten studies, the authors reported how all included study patients felt about their scar appearance at some point in time from one week to six months post-procedure. Overall, patients were satisfied with the cosmetic outcome. In two of the ten studies, the authors made direct comparisons between two types of biopsy procedures. Weber et al. compared the cosmetic results of the Mammotome with an 11-gauge needle to those of the ABBI.[108] They found the ABBI group was less satisfied with the appearance of the biopsy site than those in the Mammotome group. Chun et al. compared patients having either an ABBI or the Mammotome with an 11-gauge needle to those undergoing a wire localized biopsy.[181] These authors found that many patients in the wire localized group were unhappy with their cosmetic result, while all of the patients having Mammotome or ABBI found the scar appearance to be acceptable or excellent.
Physician experience	5 prospective studies[46,58,97,178,197] and 5 retrospective studies[198-202]	23,332	Eight of the ten included studies described the study physicians' level of experience and how that may have impacted the studies' results. In two of these cases (Schneider et al.[197] and Wunderbaldinger et al.[58]), the study investigators were testing a new CNB device and concluded that the device is suitable for physicians without a great deal of experience performing biopsies. The other two articles described how the availability of highly experienced biopsy operators has led to a decrease in the use of diagnostic excisional biopsies (Holloway et al.[198] and Hoffman et al.[199]).
Procedure time	23 prospective studies[51,58,78,96,97,100,103,106,112,124,144,158,178,179,187,194,197,203-208] and 17 retrospective studies[69,77,79,108,120,138,189,190,196,200,201,209-214]	6,121	A total of 40 studies reported procedure times for the various breast biopsy procedures. There was great variation in reported procedure times by study, with a range of between 10 and 128 minutes. Some studies indicated that changing from a conventional to an add-on unit and increased operator experience tended to decrease procedure times, while other studies suggested that cases in which benign epithelial cells were disseminated or where ABBI and wire localized procedures were used procedure times tended to be increased.
Spared procedure rates	8 prospective studies[51,103,106,112,185,186,215,216] and 23 retrospective studies[60,69,84,114,136,177,214,217-230]	8,407	31 studies reported how diagnostic CNB spared patients a surgical procedure as compared with a diagnostic excisional biopsy. CNB appears to spare a majority of patients additional surgical procedures. One particularly important finding was that women diagnosed with breast cancer by core-needle biopsy were usually able to have their cancer treated with a single surgical procedure, but women diagnosed with breast cancer by open surgical biopsy often required more than one surgical procedure to treat their cancer (odds ratio 13.7, 95% CI: 5.5 to 34.6).

Table 12. Key Question 3: other outcomes (continued)

Outcome	Number of Studies	Number of Patients	Summary of Findings
Availability of a qualified pathologist	1 prospective study[183] and 1 retrospective study[182]	2,112	Two studies addressed the availability of a qualified pathologist for interpreting biopsy specimens. The first, Collins et al., found that whether a specimen was read by a local or central pathologist made very little difference.[182] Agreement rates between the two were very high for both CNB and open biopsy, although agreement rates were somewhat lower for open biopsy specimens. The second study, Gukas et al, evaluated the accuracy of TruCut versus excisional biopsy in Nigeria.[183] The pathologist used in their study did not have a lot of experience with the TruCut device, and the authors concluded that his lack of experience explains TruCut's poor performance compared with excisional biopsy.
Availability of equipment	2 prospective studies[185,186] and 1 retrospective study[184]	5,921	Three studies addressed the availability of various breast biopsy devices. One, Deurloo et al., explained that while vacuum-assisted CNB is on the rise in the United States, in Europe automated gun CNB is the preferred technique, suggesting that European women are much less likely to have access to a vacuum-assisted procedure than are women in this country.[184] Verkooijen et al. report that median wait times, from initial physician referral to first diagnostic procedure, were shorter for patients having a CNB than those requiring an open biopsy (4 vs. 13 days, respectively), while Williams et al. found a longer wait list for prone CNB patients than for a historical cohort in the pre-prone table days.[185,186]
Resource usage	2 prospective studies[187,188]	393	Two studies addressed how the various breast biopsy techniques impact resource usage. Mainiero et al. compared the amount of physician time and room time utilized by vacuum-assisted CNB compared to freehand ultrasound-guided CNB.[187] They found the vacuum-assisted method required more physician and room time. Wunderbaldinger et al. reported that prone devices use four times the amount of hospital/office space as non-prone units.[188]
Procedure preference	12 prospective studies[100,101,106,178-180,183,192-194,231,232] and 8 retrospective studies[77,108,120,138,181,196,222,233]	5,001	Twenty studies collected data on patient preferences for breast biopsy procedures. Overall, these studies reported that patients tolerated the CNB procedure well and that a good percentage indicated they would recommend the procedure to others.
Wait time for test results	2 prospective studies[183,185]	272	Two studies reported how long it may take patients to receive a diagnosis following either a CNB or open biopsy procedure. In both studies, wait times were shorter for the CNB (7.3 days less and 9 vs. 19 days, respectively).

Table 13. Summary of economic aspects of core-needle biopsy

Aspect	N Studies	Conclusions and Comments
Relative costs open biopsy vs. core-needle biopsy	8	All report that core-needle biopsy costs less than open biopsy procedures.
Relative costs of different types of core-needle biopsy	3	Insufficient data. All three studies reported information on different comparisons.
Resource usage	2	Insufficient data. Both studies reported information on different topics.

Table 14. Summary of patient perspectives on choice of biopsy method

Aspect	N Studies	Conclusions and Comments
Procedure preference	20	The majority of the studies concluded that patients preferred core-needle procedures over open procedures
Spared surgical procedures	31	Approximately 75% of women who underwent a core-needle procedure were spared further procedures, with a mean of 1.2 procedures per woman compared to 1.5 to 2.0 procedures per woman who went straight to open biopsy.
Cosmetic results	10	Overall patients were satisfied with the cosmetic results of a vacuum-assisted core-needle procedure.
Procedure duration time	40	US-guided core-needle procedures took 10 to 60 minutes, stereotactically-guided core-needle procedures took 19 to 70 minutes, vacuum-assisted core-needle biopsies took 10 to 70 minutes. Open biopsy procedures were estimated to take 40 to 45 minutes.
Wait time for test result	2	Insufficient data

Table 15. Summary of clinician and facility factors related to core-needle biopsy

Aspect	N Studies	Conclusions and Comments
Clinician experience	10	Greater experience with particular devices improved accuracy. Some types of devices were easier for inexperienced clinicians to use than others.
Availability of Equipment	3	Insufficient data
Availability of qualified pathologists	2	Insufficient data

Previously Published Systematic Reviews

Our searches identified two previously published systematic reviews. Verkooijen et al. reviewed the literature published prior to 1999 on core-needle biopsy of non-palpable lesions.[234] Fahrbach et al. reviewed the literature published from 1996 to 2004 on core-needle biopsy of patients referred for biopsy after screening mammography.[235]

We assessed the quality of each systematic review using the 'assessment of multiple systematic reviews' (AMSTAR) measurement tool.[236] The AMSTAR consists of 11 items, which have been tested for face and content validity. The items assess whether or not a systematic review includes important elements, such as a comprehensive literature search, assessment of study quality, appropriate methods to combine study findings, and assessment of publication bias. Responses to each item are checked as 'Yes' if the review includes that item, 'No' if it does not, 'Can't tell' if the item cannot be answered by the information provided in the review, or 'Not applicable' if the item is not applicable. The AMSTAR does not provide a method for rating the quality of a review. To rate the quality of the reviews, we applied the following criteria: a rating of 'High' if the review received mostly 'yes' responses (at least 8), a rating of 'Low' if the review received mostly 'no' responses (at least 8), and a rating of 'Moderate' if the review received mixed responses. Both systematic reviews were rated as Moderate quality. The reviews were not rated as High quality because neither systematic review stated conflicts of interest or incorporated ratings of the quality of the literature into their conclusions. See Appendix E for details about the quality rating.

Verkooijen et al. included only five cohort studies in their review. Their inclusion criteria were studies of non-palpable lesions, either surgical biopsy or at least two years of followup to verify the true diagnosis, and a minimum of five cores taken per lesion. All included studies happened to have used stereotactic guidance. The authors assumed core-needle biopsy had no false-positives (i.e., malignant diagnoses on core needle that were not found on open surgery were assumed to have been completely removed by the core-needle procedure). Their analyses found that the DCIS underestimation rate was 15% (95% CI: 8.0 to 26.0%), the ADH underestimation rate was 40% (95% CI: 26.0 to 56.0%), and the overall sensitivity of core-needle biopsy for non-palpable lesions was 97.0% (95% CI: 95.0% to 99.0%). Only two complications were reported, one hematoma and one case of infection.[234]

Fahrbach et al. included 12 studies of stereotactically-guided vacuum-assisted core-needle biopsy and compared them to 25 studies of stereotactically-guided automated gun core-needle biopsy. One of their inclusion criterion was that the study must have been conducted in a western-style health care system (North America, Europe, Australia, or New Zealand). Their analyses found the false-negative rate of vacuum-assisted biopsy was 1.2%, the DCIS underestimation rate was 13.7%, and the ADH underestimation rate was 29.2%. Automated gun core-needle biopsy had a false-negative rate of 2%, a DCIS underestimation rate of 27.1%, and an ADH underestimation rate of 47.4%. Further, the authors performed analyses of possible factors that may have affected the results. Study location was a significant predictor of the false-negative rate, but type of reference standard and patient position had no significant impact on the results.

The authors of both systematic reviews concluded that core-needle biopsy rarely misdiagnosed malignant lesions as benign. Fahrbach et al. concluded that vacuum-assisted biopsy may provide lower miss and underestimation rates than automated gun core-needle biopsy.[235]

Chapter 4. Discussion

Open surgical biopsy is the "gold standard" method of evaluating a suspicious breast lesion. However, it is a surgical procedure that, like all surgeries, places the patient at risk of experiencing morbidities and, in rare cases, mortality. The majority of women who undergo breast biopsy procedures do not have cancer. Exposing large numbers of women to invasive surgical procedures when the majority of these women do not benefit from the procedure may be considered an unacceptable medical practice. A less invasive method would be preferable if it were sufficiently accurate.

Open surgical biopsy has been reported to miss 1 to 2% of breast cancers.[40] Our analysis found that stereotactically-guided vacuum-assisted core-needle biopsy is almost as accurate as open surgical biopsy with a much lower complication rate. US-guided automated gun core-needle biopsy may be almost as accurate as stereotactically-guided vacuum-assisted biopsy, and may have a slightly lower complication rate than vacuum-assisted biopsy. Both US-guided automated gun biopsy and stereotactically-guided vacuum-assisted biopsy meet the criteria of being sufficiently accurate and safer than open surgical biopsy, and therefore under most clinical conditions are preferable to open surgical biopsy. It is possible that US-guided vacuum-assisted biopsy and stereotactically guided automated gun also meet the criteria of being sufficiently accurate and safer than open surgical biopsy, but the confidence intervals around the point estimates of accuracy are too wide to be certain.

Diagnoses of "pure" DCIS determined on the basis of core-needle biopsy may be incorrect due to the inability of needle biopsy to sample all parts of the tumor. Rakha and Ellis reviewed the literature in 2007 and reported that 15 to 20% of cases diagnosed as "pure" DCIS by core-needle biopsy were subsequently found to contain associated invasive carcinoma upon excision.[16] Our analyses found that DCIS underestimation rates ranged from 13% to 36%, justifying current clinical practice of referring all DCIS diagnoses for open surgery.

The management of "high risk" lesions such as ADH is somewhat controversial. Our analysis found that at least 20% of ADH diagnoses on core-needle biopsy are actually malignant, suggesting that some patients diagnosed with atypia on core needle may benefit from open surgery as well.

In Figure 5E, in the Executive Summary, we present a simple model of what might happen if the same cohort of 1000 women underwent various types of breast biopsy. The cohort of women includes 300 women with malignant tumors, and 700 women with benign lesions. The model is based on the point estimates of accuracy from our analyses and do not incorporate estimates of uncertainty in the point estimates. Refer to Figure 1 A through Figure 4 D in the Executive Summary for a visual representation of the degree of uncertainty in the point estimates.

Limitations of the Evidence Base

The evidence base is very large but of generally low quality. The majority of the available studies are poorly reported retrospective chart reviews. Most of the studies included all patients who underwent core-needle biopsy at a particular center or centers during a certain time period and had no other inclusion criteria for enrollment. Very few studies reported any characteristics of their patients; some did not even report how many patients were enrolled. Details of operator training and experience were often omitted, as were details about the training

and experience of the pathologists reading the biopsy material. Many studies combined results for multiple core-needle biopsy methods. Others changed biopsy methodology in mid-study. Descriptions of biopsy methods were often inadequate. Characteristics of the breast lesions being biopsied were often omitted. Biopsy diagnoses were often collapsed into "benign" and "malignant" categories, instead of being presented in a more granular form by type of lesion. Sources of funding for the studies were usually not mentioned. Presentation of results was often haphazard and confusing. Many patients diagnosed as "benign" on core-needle biopsy had inadequate followup data. Poor reporting of biopsy methodology, patient characteristics, and details of lesions precluded answering the majority of the sub-questions about factors affecting the accuracy and harms of core-needle biopsy.

Applicability

We used inclusion criteria intended to restrict the evidence base to only those studies that included the population of interest: women of average risk undergoing breast biopsy after discovery of a suspicious lesion on routine screening. However, our analysis found that the prevalence of cancers in the study populations tended to be slightly higher than expected. The prevalence of cancers in the general population sent for breast biopsy (in the USA) has been reported to be around 23%.[15] The studies in our analysis generally reported prevalence in the thirties to forties, and up to 55% for freehand biopsies. This may be due to the fact that many of the studies were conducted in non-USA locations, where the prevalence of cancers in populations sent for biopsy has been reported to be 60 to 70%.[234] It may also be an artifact caused by attrition. Many of the studies had fairly high rates of attrition, and most of the lost patients had been diagnosed as benign on core-needle biopsy. The lost patients were of necessity removed from the analysis, and this may have artificially elevated the prevalence of disease. Interestingly, the studies of US-guided vacuum-assisted biopsy reported an overall prevalence of disease of only 15%, suggesting that lesions selected for this method may have a low probability of being malignant. Lesions selected for US-guided procedures generally do not contain microcalcifications and must be clearly visible on US.

Possible Impact of Key Assumptions on the Conclusions

Several key assumptions were made: (1) the "reference standard", a combination of open surgery and followup for at least six months, was 100% accurate; (2) the pathologists examining the open surgical biopsy results were 100% accurate; and (3) core-needle diagnoses of malignancy (invasive or in situ) that could not be confirmed by open surgery were assumed to have been correct diagnoses where the lesion had been completely removed by the core-needle biopsy procedure. In addition, the majority of studies reported data on a per-lesion rather than a per-patient basis, and therefore we analyzed the data on a per-lesion basis.

Key assumption #1, that the reference standard was 100% accurate, is almost certainly not true. Open surgical biopsy has been reported to have a false-negative rate of 1 to 2% when two years of patient followup was used as the reference standard.[40] If a small percentage of the surgical biopsies were false-negatives then our estimates of the accuracy of core-needle biopsy are slightly lower than the actual "true" accuracy of core-needle biopsy. If a small percentage of the patients declared "benign" on six-month patient followup actually had cancers then our estimates of the accuracy of core-needle biopsy are higher than the actual "true" accuracy of core-needle biopsy. Logically one would expect short-term patient followup to be more prone to error than open surgical biopsy; thus it seems likely that our estimates of core-needle biopsy

accuracy are slightly higher than the actual "true" accuracy. However, some of the studies did follow all patients for at least two years, and other studies did perform open biopsy on all patients. We performed meta-regressions and found no statistically significant impact of the type of reference standard used or length of followup on the reported accuracy of the core-needle biopsies.

Key assumptions #2 and #3 are inter-related and both depend on pathologists being 100% accurate in reading open surgical biopsy material. The errors that pathologists make when examining core-needle biopsy specimens are incorporated into our conclusions about the accuracy of core-needle biopsy: causes of misdiagnosis include errors of sampling as well as errors of pathologists examining the core-needle specimens. The literature reports pathology errors in general as being rare, affecting 0.08 to 1.2% of specimens examined.[237] The fact that open surgical biopsy has a false-negative rate of less than 2% also suggests that open surgical biopsy pathology errors are quite rare; this low false-negative rate includes errors of surgery as well as errors of pathologists. A 2006 review of medical malpractice suits filed against pathologists for breast biopsy misdiagnoses reported that about half the suits involved false-negative errors and about half involved false-positive errors.[237] Even if a very small percentage of patients declared "true positive" in our analysis were actually false-positives and a very small percentage of patients declared "true negatives" were actually false-negatives, it seems unlikely that our estimates of core-needle biopsy accuracy can be significantly different than the actual true accuracy. The clinical impact of pathology errors, however, is not insignificant, since it can lead to over- and under- treatment.

Key assumption #4, that analyzing the data on a per-lesion rather than a per-patient basis would not violate statistical assumptions of independence, was unavoidable. Very few of the studies reported data on a per-patient basis. The percentage of patients with more than one lesion was, in most studies, quite low. Each lesion was subjected to an independent core-needle biopsy. A patient diagnosed with multiple benign lesions would have all lesions managed by followup, but a patient with one malignant lesion and a benign lesion may have had the benign lesion surgically biopsied at the same time as the malignant lesion was biopsied. Thus the independence of data at the per-lesion level is not quite complete. The impact of this minor lack of independence on the results of our analyses is most likely insignificant.

Correlation With Findings From Prior Systematic Reviews

As discussed previously, two prior systematic reviews of core-needle biopsy have been published.[234,235] Both prior reviews and our review calculated very similar false-negative rates for stereotactically-guided automated gun core-needle biopsy: 2.2%, 3.0%, and 2.0%.
Both prior reviews and our review calculated very similar rates of ADH underestimation for stereotactically-guided automated gun core-needle biopsy: 40%, 43.5%, and 47.4%. The DCIS underestimation rate reported by Verkooijen et al. for stereotactically-guided core-needle biopsy was much lower (only 15.0%) than the DCIS underestimation rates reported by Fahrbach et al. and our review (24.4%, 27.1%, respectively). This difference may be related to the fact that our review and Fahrbrach et al. included both palpable and non-palpable lesions in the analysis whereas Verkooijen et al. restricted their analysis to non-palpable lesions.

Verkooijen et al. did not study stereotactically-guided vacuum-assisted core-needle biopsy. Our review and Fahrbach et al. found very similar accuracy figures for stereotactically-guided vacuum-assisted core-needle biopsy: false negative rate, 1.2% and 0.8%; ADH underestimation rate, 29.2% and 21.9%; DCIS underestimation rate, 13.7% and 13.0%.

Fahrbach et al. found that study location was a significant predictor of the false-negative rate, but type of reference standard and patient position had no significant impact on the results. We also found that the type of reference standard had no impact on the results, but we found no impact of study location on the results. The reason for this apparent discrepancy may be that we included studies conducted worldwide, whereas Fahrbach et al. included only studies conducted in North America, Europe, Australia, or New Zealand.

Future Research Needed

For many interventions, randomized controlled trials that measure patient-oriented outcomes are necessary in order to justify the routine use of the intervention. However, it is generally believed that early diagnosis and treatment of breast tumors leads to improved survival rates and quality of life. Women found to have benign lesions on biopsy are able to avoid unnecessary treatment and receive reassurance that they do not have breast cancer. There is no need to conduct randomized controlled trials reporting patient-oriented outcomes of breast biopsy procedures. Establishing that a type of breast biopsy is safer than open surgical biopsy while being as or almost as accurate as open surgical biopsy is sufficient to justify its routine use. Our systematic review has found that both stereotactically guided vacuum-assisted and US-guided automated gun core-needle biopsy are safer than open surgical biopsy and are almost as accurate as open surgical biopsy, justifying their routine use.

However, well-reported retrospective chart reviews, retrospective database analyses, or prospective diagnostic accuracy studies are needed to address the as-yet-unanswered questions as to what factors affect the accuracy and harms of core-needle breast biopsy. We have listed the most important as-yet unanswered questions in Table 16. Answers to such questions are important for both patients and clinicians when faced with the decision of what type of breast biopsy is best for each individual patient. The unanswered questions can be addressed by a prospective or retrospective diagnostic cohort study that reports relevant information in a format that allows each unanswered question to be directly addressed. It is possible that many of the studies included in the current systematic review collected information that addressed some of the unanswered questions but did not report it.

In addition, our conclusions are often rated as being supported by a low strength of evidence. The low rating is almost entirely due to the fact that the evidence base, while large, consists of universally poorly reported studies. The studies omitted important details about patients, methods, and results. The studies presented results in an often confusing and haphazard manner. The poor reporting made it difficult to determine whether the studies were likely to be unaffected by bias, and therefore we rated the evidence base as being of low quality. Publication of better-reported diagnostic accuracy studies would permit verification that our conclusions are accurate and not influenced by biases in the studies included in this technology assessment.

Table 16. Unanswered questions

Unanswered questions about accuracy
What is the accuracy of MRI-guided core-needle biopsy?
What impact does patient age have on the accuracy of different methods of performing breast biopsy?
What impact does breast density have on the accuracy of different methods of performing breast biopsy?
What impact do patient co-morbidities have on the accuracy of different methods of performing breast biopsy?
Do different methods of breast biopsy have different accuracies for palpable vs. non-palpable lesions, microcalcifications vs. masses, distortions vs. masses?
What impact does the size of the lesion have on the accuracy of different methods of performing breast biopsy?
What impact does the location of the lesion have on the accuracy of different methods of performing breast biopsy?
What impact does the number of cores taken have on the accuracy of different methods of performing breast biopsy?
What impact does patient positioning have on the accuracy of different methods of performing breast biopsy?
What impact does experience of the operator have on the accuracy of different methods of performing breast biopsy?
What impact does the training of the operator have on the accuracy of different methods of performing breast biopsy?
Unanswered questions about harms
What impact does the type of image guidance (none, MRI, stereotactic, or US) have on adverse events of breast biopsy?
What impact does patient age have on adverse events related to breast biopsy?
What impact does breast density have on adverse events of breast biopsy?
What impact do patient co-morbidities have on adverse events of breast biopsy?
Does the type of lesion- palpable vs. non-palpable lesions, microcalcifications vs. masses, distortions vs. masses- have an impact on adverse events of breast biopsy?
What impact does the size of the lesion have on adverse events of breast biopsy?
What impact does the location of the lesion have on adverse events of breast biopsy?
What impact does the number of cores taken have on adverse events of breast biopsy?
What impact does the needle size have on adverse events of breast biopsy?
What impact does experience of the operator have on adverse events of breast biopsy?
What impact does the training of the operator have on adverse events of breast biopsy?
What impact does the facility location or type of facility have on adverse events of breast biopsy?
Unanswered questions about economic aspects
What impact does the cost of different types of core-needle breast biopsy have on the choice to perform a particular type of breast biopsy?
What impact does the availability of equipment and resources have on the choice to perform a particular type of breast biopsy?
What impact does the availability of a qualified pathologist have on the choice to perform a particular type of breast biopsy?

References and Included Studies

(Note: There is a separate set of references at the end of Appendix G whose reference numbers are different from those in the text of the report.)

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List of Acronyms/Abbreviations

ADH	Atypical Ductal Hyperplasia
AHRQ	Agency for Healthcare Research and Quality
ALH	Atypical Lobular Hyperplasia
BI-RADS®	Breast Imaging Reporting and Data System
CI	Confidence Interval
DCIS	Ductal Carcinoma In Situ
FN	False Negative
FP	False Positive
G	Gauge
LCIS	Lobular Carcinoma In Situ
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NR	Not Reported
TN	True Negative
TP	True Positive
UK	United Kingdom
US	Ultrasound
USA	United States of America

Glossary of Selected Terms

Atypical ductal hyperplasia (ADH). A condition in which the cells that line the milk ducts of the breast experience abnormal growth. The lesion itself is not malignant but may sometimes contain foci of malignant cells and women with ADH have an elevated risk of developing a malignant lesion.

Automated biopsy gun. A device used to obtain core-needle samples. The device is pressed against the tissue at the appropriate location and angle and then the needle is "fired" into the tissue. After confirming the core-needle has sampled the appropriate tissue the needle is withdrawn and the tissue sample ejected from the needle into a sampling container. Some units use a coaxial needle. With a coaxial needle, a cannula (hollow tube) is advanced into the tissue until in contact with the area to be sampled, and then the sampling needle is "fired" through the cannula and into the lesion.

Ductal carcinoma in situ (DCIS). A carcinoma of the milk ducts of the breast that is confined within the duct.

High-risk lesion. Any of a number of different types of non-cancerous lesions of the breast that have been observed to sometimes contain foci of malignant cells, and women diagnosed with these types of lesions have an elevated risk of developing a malignant lesion. Some common types of high-risk lesions include atypical ductal hyperplasia (ADH), radial scars, papillary lesions, atypical lobular hyperplasia (ALH), and lobular carcinoma in situ (LCIS).

Microcalcification. A tiny deposit of calcium visible as a bright spot on a mammogram. Tight clusters of microcalcifications may be a sign of a malignant lesion.

Negative likelihood ratio. A measure of the ability of the diagnostic test to accurately "rule out" disease. The smaller the negative likelihood ratio is, the more accurate the test is.

Palpable lesion. A breast lesion that can be felt by manual manipulation.

Sensitivity. Sensitivity is the proportion of people with the disease who have a positive test for the disease. A test with high sensitivity will rarely misclassify people with the disease as not having the disease (the test has a low rate of false-negatives).

Stereotactic guidance. X-rays are taken from multiple locations in order to accurately identify the exact location of the lesion to be sampled. After using the images to determine where to sample, the needle is inserted. Further x-ray images are usually taken to confirm the needle has penetrated the lesion.

Ultrasound guidance. High-frequency sound waves are used to visualize the exact location of the lesion to be sampled. After using the images to determine where to sample, the needle is inserted. Images can be taken continuously during needle insertion to guide and confirm the needle has penetrated the lesion.

Vacuum-assisted. After insertion of a hollow biopsy needle a vacuum can be applied to pull tissue into the needle.

Underestimation rate. The percentage of lesions that were diagnosed on core-needle biopsy as lesion types of lesser concern than the final diagnosis. For example, a lesion diagnosed as ADH on core-needle biopsy that is diagnosed as malignant on open biopsy was “underestimated” by the core-needle biopsy.