



Complete Summary

GUIDELINE TITLE

The role of aromatase inhibitors in adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Eisen A, Trudeau M, Shelley W, Sinclair S, Breast Cancer Disease Site Group. The role of aromatase inhibitors in adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 Feb 26. 49 p. (Evidence-based series; no. 1-18). [86 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Early-stage, hormone receptor-positive breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

In postmenopausal women with early-stage, hormone receptor-positive breast cancer:

- To evaluate if adjuvant aromatase inhibitors (anastrozole, letrozole, or exemestane) alone for five years compared with adjuvant tamoxifen alone for five years, improve clinically meaningful outcomes (disease-free or overall survival)
- To evaluate if adjuvant aromatase inhibitors in sequence with tamoxifen for a total of five years compared with adjuvant tamoxifen alone for five years, improve clinically meaningful outcomes
- To evaluate if aromatase inhibitors after five years of adjuvant tamoxifen therapy compared with placebo, improve clinically meaningful outcomes
- To evaluate the harms associated with aromatase inhibitors compared with tamoxifen or placebo
- To evaluate if the efficacy of aromatase inhibitors depend on p185^{HER2/neu} glycoprotein expression, compared with tamoxifen

TARGET POPULATION

Postmenopausal women with early-stage, hormone receptor-positive breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Adjuvant tamoxifen alone for 5 years
2. Adjuvant aromatase inhibitors (anastrozole, letrozole, or exemestane) alone and in sequence with tamoxifen
3. Monitoring changes in bone mineral density and other harms of aromatase inhibitors
4. Predicting response to treatment based on HER2/*neu* status (considered but no recommendation made)

MAJOR OUTCOMES CONSIDERED

- Disease-free survival

- Overall survival
- Adverse events
- Menopausal symptoms
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

MEDLINE was searched through to May 9, 2007 using a disease-specific medical subject heading (MeSH) descriptor ("breast neoplasms"), a treatment-specific descriptor ("chemotherapy, adjuvant"), and agent-specific descriptors ("aromatase/antagonists and inhibitors"). The Excerpta Medica database (EMBASE) was also searched through to May 9, 2007 using a disease-specific Excerpta Medica Tree (EMTREE) term ("breast cancer"), a treatment-specific keyword ("adjuvant chemotherapy"), and agent-specific terms ("anastrozole" or "letrozole" or "exemestane"). These terms and various synonyms were then combined with search terms for the following publication types: randomized controlled trial, systematic review, or meta-analysis.

The Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews were also searched through to May 9, 2007. Online conference proceedings from the American Society of Clinical Oncology (ASCO) Annual Meetings from 1999 to 2006 (<http://www.asco.org>) and the San Antonio Breast Cancer Symposia from 2001 to 2006 (<http://www.sabcs.org>) were also searched.

Relevant articles and abstracts were selected by one reviewer. The reference lists from all sources were searched for additional trials.

Study Selection Criteria

Articles were selected for inclusion in this systematic review, based on the following criteria:

- Third-generation aromatase inhibitors (anastrozole, letrozole, or exemestane) as adjuvant therapy were evaluated in a randomized controlled trial or meta-analysis.
- Trial primary outcomes included disease/event/relapse-free survival and/or overall survival.
- Clinical trial results were reported in full papers or abstracts.

Non-English trials were excluded, as transition capabilities were not available. Also, in order to concentrate on the most relevant data, trials designed solely to study toxicity or quality of life with no efficacy outcome were excluded from data abstraction, although their references are reported in the original guideline document.

NUMBER OF SOURCE DOCUMENTS

Nine randomized controlled trials and one meta-analysis were eligible for inclusion in this systematic review. An additional three trials with efficacy primary outcomes have reported quality of life and/or toxicity data but have not yet reported efficacy data; these trials are described in the original guideline document.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview © Update Software) was used to create forest plots of time-to-event data. When necessary and possible, hazard ratios and confidence intervals for disease-free and overall survival were derived from reported data using the methods described by Parmar et al.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

For a complete discussion of the methods used to formulate the recommendations, please refer to the "Discussion" section of the original guideline document.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Following review and discussion of Sections 1 and 2 of this evidence-based series, the Breast Cancer Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Practitioner feedback was obtained through a mailed survey of 127 practitioners in Ontario (74 medical oncologists, 33 radiation oncologists, and 20 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on October 4, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer DSG reviewed the results of the survey.

The final Evidence-based Series report was reviewed and approved by one member of the Program in Evidence-based Care (PEBC) Report Approval Panel with expertise in clinical and methodology issues.

February 2008 Update to Evidentiary Base

In response to comments made by the *Cancer Treatment Reviews* editor during a process for manuscript publication, the evidentiary base was updated to May 2007 (and accepted for publication in January 2008). The process primarily provided updated results for data previously presented in abstract form, and no new trials of significant relevance were identified. As the February 2008 revision did not significantly alter the recommendations of the October 2005 practice guideline, no internal (report approval) or external (practitioner feedback) review was undertaken. All updated components were, however, reviewed by all authors of the practice guideline and approved by the Breast Cancer DSG during an annual consensus meeting.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommended treatment options for postmenopausal women with hormone receptor-positive early breast cancer:

Available trial evidence supports six adjuvant hormonal therapy options, summarized across four recommendations directly below, for the treatment of the target population. At present, there are no data available to compare between the various adjuvant aromatase inhibitor strategies. Rather, the use of adjuvant aromatase inhibitors has been compared to the standard of five years of adjuvant tamoxifen. Therefore, the decision about which therapy option to consider for patients beginning hormonal therapy should be made on an individual patient basis. Key evidence and qualifying statements in support of the recommendations will follow the recommendations and proceed in a similar order.

1. Adjuvant tamoxifen (20 mg daily for five years) remains an acceptable option for the treatment of women with hormone receptor-positive, early-stage breast cancer.
2. Adjuvant anastrozole (1.0 mg daily for five years) or letrozole (2.5 mg daily for five years) is an acceptable alternative to five years of adjuvant tamoxifen therapy.
3. Adjuvant tamoxifen (20 mg for two to three years) followed by switching to either adjuvant exemestane (25 mg daily, to a total of five years of hormone therapy) or adjuvant anastrozole (1 mg daily, to a total of five years) therapy is also an acceptable alternative to five years of tamoxifen.
4. Adjuvant letrozole (2.5 mg daily for five years) should be considered for women who have completed five years of adjuvant tamoxifen therapy.

Precautions

5. Women receiving aromatase inhibitors should be monitored for changes in bone mineral density.

Predictors of Treatment Response

6. Due to the lack of evidence, no recommendation for the use of aromatase inhibitors based on human epidermal growth factor receptor 2 (HER2)/*neu* status can be made at this time.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and one meta-analysis.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- The Arimidex (anastrozole) or Tamoxifen Alone or in Combination (ATAC) study (n=9,366) compared tamoxifen versus anastrozole versus tamoxifen plus anastrozole. At 68 months (5.7 years), disease-free survival was significantly improved in the anastrozole group versus the tamoxifen group (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78 to 0.97; p=0.03). The absolute difference in four-year disease-free survival estimates was 2.4% (86.9% with anastrozole versus 84.5% with tamoxifen). Additional benefit was seen for time to recurrence (TTR) and time to distant recurrence (TDR) with anastrozole. Overall survival was not significantly different.
- The Breast International Group (BIG) 1-98 trial compared letrozole versus tamoxifen in 8,028 women. After a median follow-up of 51 months, patients treated with letrozole had significantly better disease-free survival (primary endpoint) versus those treated with tamoxifen (HR, 0.82; 95% CI, 0.71 to 0.95). There was also significant benefit for TTR and TDR with letrozole. Overall survival was not significantly different.
- The Intergroup Exemestane Study (n=4,742) compared two to three years of tamoxifen followed by exemestane with two to three years of tamoxifen followed by further tamoxifen, each to a total of five years of adjuvant hormone therapy. At 55.7 months median follow-up, the exemestane arm showed significantly improved disease-free survival (HR, 0.76; 95% CI, 0.6 to 0.88) but showed no significant benefit for overall survival. Time to contralateral breast cancer, TTR, and TDR were also significantly improved in women who switched to exemestane. Overall survival was significantly improved only during a subgroup analysis that excluded patients with estrogen receptor-negative disease (HR, 0.83; 95% CI, 0.69 to 1.00 in favour of switching to exemestane).
- The Italian Tamoxifen Arimidex (anastrozole) (ITA) trial (n=426) compared tamoxifen (20 mg daily) for two or more years followed by further tamoxifen or anastrozole (1.0 mg daily) to a total of five years of adjuvant hormone therapy. At 64 months follow-up, disease-free survival (primary endpoint) was significantly improved in women who switched to anastrozole (HR, 0.57; 95% CI, 0.38 to 0.85). There was no significant difference in overall survival between therapy arms.
- The Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 and German Adjuvant Breast Cancer Group Arimidex/Nolvadex (ARNO)-95 trials had arms identical to the ITA trial described above. At 28-months median follow-up, a combined analysis showed significantly improved disease-free survival for women who switched to anastrozole (HR, 0.60; 95% CI, 0.44 to 0.81). Distant metastases-free survival was also significantly longer with anastrozole (HR, 0.61; 95% CI, 0.42 to 0.87). There was no significant difference in overall survival.
- A meta-analysis of the ABCSG-8, ARNO-95, and ITA trials found improvements in disease-free survival (HR, 0.59; 95% CI, 0.48 to 0.74; p<0.0001), distant recurrence-free survival (HR 0.61, 95% CI 0.45 to 0.83, p=0.002), and overall survival (HR, 0.71; 95% CI, 0.52 to 0.98; p=0.04) for women who switched to anastrozole.
- The MA.17 study (n=5,187) compared letrozole to placebo following 4.5 to six years of tamoxifen. In an interim analysis at 2.4 years, there was an improvement in disease-free survival favouring letrozole over placebo (HR, 0.57; 95% CI, 0.43 to 0.75; p=0.00008). The estimated four-year, disease-free survival rates were 93% with letrozole versus 87% with placebo (6% absolute difference). The final analysis at 2.5 years continues to show improved rates of recurrence (42% reduction in risk, p=0.0004). In the whole

sample, overall survival was not significantly different at either analysis. In the final analysis, overall survival was significantly improved with letrozole in node-positive women (HR, 0.61; 95% CI, 0.38 to 0.98; $p=0.04$) and in those who received more than five years of tamoxifen (HR, 0.56; 95% CI, 0.33 to 0.97; $p=0.04$) but not in node-negative women (HR, 1.52; 95% CI, 0.76 to 3.06; $p=0.24$). Additional abstracts report on data at 4.5 years of median follow-up, at which time 73% of the placebo arm had crossed over to letrozole. Results indicate continued benefit in disease-free survival, but not overall survival, for all patients treated with letrozole including for those who had crossed over.

- A randomized trial comparing four months of neoadjuvant tamoxifen with letrozole in postmenopausal women with breast cancer ineligible for conservation surgery reported superior overall response rates in the letrozole group (60% vs. 41%; $p=0.004$). In human epidermal growth factor receptor 2 (HER2)/*neu*-overexpressing women, response rates were 88% and 21%, respectively ($p=0.0004$). Conversely, in HER2/*neu*-normal women, respective response rates were 54% and 42% ($p=0.078$).
- In two trials where the primary outcome was the proliferation marker Ki67, HER2/*neu*-overexpressing women with operable breast cancer experienced greater reductions in Ki67 compared with HER2/*neu*-normal women; however, the difference was statistically significant in only one trial.

POTENTIAL HARMS

- Compared with tamoxifen alone, evidence from the Arimidex (anastrozole) or Tamoxifen Alone or in Combination (ATAC) and Breast International Group (BIG) 1-98 trials indicate a higher incidence of fracture for aromatase inhibitors alone (11.0% vs. 7.7%, $p<0.0001$ for anastrozole alone; 8.6% vs. 5.8%, $p<0.001$ for letrozole alone), and greater decline in both lumbar spine mineral density (-8.1% [95% confidence interval (CI) -10.1% to -6.1%, $p<0.0001$) and hip bone mineral density (-7.4% [95% CI -9.6% to -5.3%, $p<0.0001$) for patients treated with anastrozole alone. However, no patient in the ATAC trial with normal bone density at outset developed osteoporosis after five years of anastrozole.
- A Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) International trial substudy also indicated that patients treated with exemestane alone experienced a mean decrease of -0.24 ($p=0.02$) and -0.25 ($p=0.005$) for spine and hip bone mineral density in comparison to tamoxifen alone.
- When switching to an aromatase inhibitor after two to three years of tamoxifen was compared to continued tamoxifen, evidence from the Intergroup Exemestane Study (IES), and Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 and German Adjuvant Breast Cancer Group Arimidex/Nolvadex (ARNO)-95 trials indicate a higher incidence in fracture (7.0% vs. 4.9%, $p=0.003$ for exemestane; 2% vs. 1%, $p=0.015$ for anastrozole), osteoporosis (9.2% vs. 7.2%, $p=0.01$ for exemestane), and a greater decline in lumbar spine and hip bone mineral density (-1.4%, 95% CI -0.8% to -1.9%; and -2.7%, 95% CI -2.0% to -3.4%; respectively for exemestane at six months).
- Additional evidence from the MA.17 trial indicates a higher incidence of osteoporosis (8.1% vs. 6.0%, $p=0.003$) in women placed on letrozole following five years of tamoxifen compared to placebo.

- Due to theoretical concerns and the lack of long-term data, clinical cardiac outcomes and lipid profile changes, as well as other harms associated with aromatase inhibitors, should be monitored.
- Compared with placebo, letrozole may adversely affect quality of life and increase the occurrence of arthritis and/or arthralgia. Further evidence across various trials suggests that aromatase inhibitors increase the occurrence of arthralgia regardless of comparison group and mode of treatment.

CONTRAINDICATIONS

CONTRAINDICATIONS

Aromatase inhibitors are contraindicated for premenopausal women.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Tamoxifen remains an acceptable therapy option for several reasons. First, to date there has been no overall survival benefit detected for the use of anastrozole or letrozole alone over tamoxifen alone. Though a meta-analysis of trials indicated potential significant benefit in overall survival for switching to anastrozole in comparison to continued tamoxifen, consistent advantage in overall survival has not been observed, particularly for other aromatase inhibitors and in other treatment settings. Second, evidence indicates that patients treated with aromatase inhibitors experience a greater incidence of fractures and a greater loss of lumbar spine and hip bone mineral density (the latter specific to anastrozole; see Recommendation #5 in the 'Major Recommendations' field).
- Switching to aromatase inhibitors following less than two years of adjuvant tamoxifen therapy:

Women in the Intergroup Exemestane Study (IES), Italian Tamoxifen Arimidex (ITA), and Austrian Breast and Colorectal Cancer Study Group (ABCSCG)-8 and Arimidex/Nolvadex (ARNO)-95 trials received tamoxifen for at least two years, to three years maximum. Decisions regarding initiating aromatase inhibitors in those women who have taken tamoxifen for less than two years will have to be individualized, and there is no evidence to support a decision process at this time.

- Use of aromatase inhibitors following five years of adjuvant tamoxifen:

Patients in the MA.17 trial were treated within three months of stopping tamoxifen and had received tamoxifen for 4.5 to six years. Decisions regarding the initiation of letrozole therapy in women who have been off tamoxifen for more than three months will have to be individualized, based on the time since tamoxifen was discontinued, the prognosis of the patient, and the toxicity of treatment. Similarly, decisions regarding the initiation of letrozole in those who have taken tamoxifen for three to 4.5 years will have to be individualized.

- There is not enough evidence to evaluate the use of exemestane or anastrozole following five years of tamoxifen. The ABCSG-6a trial was developed as a continuation of the ABCSG-6 trial and compared three years of anastrozole or no further treatment following five years of adjuvant tamoxifen. At 60 months median follow-up, this trial, reported in abstract form, found significantly better disease-free survival in patients treated with anastrozole after five years of tamoxifen, with or without aminoglutethimide. No difference in overall survival was reported. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33 trial was amended to compare five years of exemestane or placebo following five years of adjuvant tamoxifen. After the release of the MA.17 results, accrual was halted, the trial was unblinded, and placebo patients were offered exemestane. At 30 months median follow-up, an abstract reported no significant difference in disease-free or overall survival.
- Data on clinical cardiac outcomes and lipid profile changes are mixed. Adverse effects on lipids in some of the aromatase inhibitor trials may be due to the discontinuation of the protective effect of tamoxifen. Due to theoretical concerns and the lack of long-term data, clinical cardiac outcomes and lipid profile changes, as well as other harms associated with aromatase inhibitors, should be monitored.
- Evidence exists to suggest that aromatase inhibitors reduce the occurrence of venous thromboembolic and gynecologic events.
- Compared with placebo, letrozole may adversely affect quality of life and increase the occurrence of arthritis and/or arthralgia. Further evidence across various trials suggests that aromatase inhibitors increase the occurrence of arthralgia regardless of comparison group and mode of treatment.
- Aromatase inhibitors are contraindicated in premenopausal women.
- No eligible trials on the efficacy of aromatase inhibitors according to human epidermal growth factor receptor 2 (HER2)/*neu* status in the adjuvant setting were identified.
- A randomized trial comparing four months of neoadjuvant tamoxifen with letrozole in postmenopausal women with breast cancer ineligible for conservation surgery reported superior overall response rates in the letrozole group (60% vs. 41%; $p=0.004$). In HER2/*neu*-overexpressing women, response rates were 88% and 21%, respectively ($p=0.0004$). Conversely, in HER/*neu*-normal women, respective response rates were 54% and 42% ($p=0.078$).
- In two trials where the primary outcome was the proliferation marker Ki67, HER2/*neu*-overexpressing women with operable breast cancer experienced greater reductions in Ki67 compared with HER2/*neu*-normal women; however, the difference was statistically significant in only one trial.

General Disclaimer

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IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Eisen A, Trudeau M, Shelley W, Sinclair S, Breast Cancer Disease Site Group. The role of aromatase inhibitors in adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 Feb 26. 49 p. (Evidence-based series; no. 1-18). [86 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Oct 25 (revised 2008 Feb 26)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Breast Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Breast Cancer DSG disclosed potential conflicts of interest relating to the topic of this practice guideline. Two of the lead authors (A. Eisen, M. Trudeau) reported related research involvement. These authors reported receiving honoraria or consultant fees from pharmaceutical companies that manufacture the aromatase inhibitors covered by this review.

GUIDELINE STATUS

This is the current release of the guideline.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of aromatase inhibitors in adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: guideline recommendations. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2008 Feb. 6 p. (Practice guideline; no. 1-18). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 24, 2006. The information was verified by the guideline developer on February 23, 2006. This summary was updated by ECRI Institute on July 17, 2008. The updated information was verified by the guideline developer on August 20, 2008.

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Date Modified: 10/27/2008

