

Methodology Supplement

TITLE: USE OF BIOMARKERS TO GUIDE DECISIONS ON ADJUVANT SYSTEMIC THERAPY FOR WOMEN WITH EARLY-STAGE INVASIVE BREAST CANCER: FOCUSED UPDATE OF 2016 AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE GUIDELINE

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1. OVERVIEW: GENERAL PRINCIPLES FOR ALL ASCO GUIDELINE PRODUCTS (e.g. de novo, Update, Endorsement, Adaptation, Provisional Clinical Opinion, Non-substantive Brief Update)

Clinical practice guidelines are systematically developed statements that assist practitioners and patients in making decisions about care. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, utilization of clinical guidelines may provide:

1. Improvements in outcomes
2. Improvements in medical practice
3. A means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas where future research is needed

Expert Panel Composition

The ASCO Clinical Practice Guidelines Committee (CPGC) and the ASCO Breast Cancer Guideline Advisory Group (GAG) convened an Expert Panel with multidisciplinary representation in medical oncology, radiation oncology, community oncology, statistician, and health outcome researchers, the Practice Guidelines Implementation Network, and patient/advocacy representation. The Expert Panel was led by two Co-Chairs who had the primary responsibility for the development and timely completion of the guideline. The Panel had two webinars and email correspondence. The Co-Chairs and ASCO staff prepared a draft guideline for review and rating by the Expert Panel. The Expert Panel members are listed in Appendix Table A1 (online only).

Guideline Development Process

The Expert Panel on several occasions and corresponded frequently through e-mail; progress on guideline development was driven primarily by the Co-Chairs/Steering Committee along with ASCO staff. The purpose of the meetings was for members to contribute content, provide critical review, interpret evidence, and finalize the guideline recommendations based upon the consideration of the evidence.* All members of the Expert Panel participated in the preparation of the draft guideline document, which was then disseminated for external review

and submitted to the *Journal of Clinical Oncology (JCO)* for peer review and consideration for publication. All ASCO guidelines are reviewed and approved by the ASCO Clinical Practice Guideline Committee prior to publication.

**If Consensus Methods were used, then:* The Expert Panel was supplemented by additional experts recruited to rate their agreement with the drafted recommendations as part of the consensus process. The entire membership of experts is referred to as the Consensus Panel. The Co-Chairs/Steering Committee and ASCO staff prepared a draft guideline for review and rating by the Consensus Panel.

Revisions - The SIGNALS Approach to Guideline Updating

At annual intervals, the Expert Panel Co-Chairs and two Committee members designated by the Co-Chairs will determine the need for revisions to the guideline based on an examination of current literature. If necessary, an Expert Panel will be (re)convened to discuss potential changes. When appropriate, the Expert Panel will recommend revised guidelines to the Clinical Practice Guideline Committee (CPGC) for review and approval.

The ASCO CPGC's Methods Subcommittee approved use of a "signals" approach to facilitate guideline updating. This approach outlines formal criteria for identifying new, practice-changing data—signals—that might translate into revised practice recommendations.

The threshold for embarking on ASCO guideline updates that translate into new or revised recommendations—the presence of a signal in the literature—is high. Two major categories of changes are recognized as potential signals:

- a potentially invalidating change in evidence: opposing findings, evidence of substantial harm, evidence of a superior new treatment; and
- A major change in evidence: important changes in efficacy but not opposing findings, expansion of treatment such as evidence of efficacy in a new population, important caveat.
- Of note, there can be reasons other than the scientific literature to initiate a guideline update, including regulatory decisions that affect existing practice recommendations and can require rapid, ad hoc updates.

As described in the following steps, the signals approach relies on a combination of literature searching and expert opinion to inform the need for guideline updating.

Step 1: Reviewing the protocol that was used for the previous systematic review.

Expert Panel leadership, in consultation with other content experts if needed, should review the currency and validity of the guideline clinical questions, target population, interventions, and outcomes. If any of these components of the protocol are out-of-date, the protocol should be revised by the Expert Panel leadership prior to the literature review.

Step 2: Completing the formal literature review and seeking Expert Panel input.

Staff members conduct annual literature searches and review the search yield in consultation with the Expert Panel leadership to identify—or to rule out—signals for updating a guideline. The sources to mine for signals in the published literature include (a) PDQ information summaries, (b) PubMed, and (c) the National Guideline Clearinghouse. The results of the literature search and the initial determination regarding the presence or absence of signals are distributed to the Expert Panel for comment. The Co-Chairs/Steering Committee may also choose to survey the Expert Panel regarding the presence or absence of signals (see Figures 1 and 2).

Step 3: Choosing the updating option.

Expert Panel leadership makes the final decision on the type of guideline update to issue.

There are three basic updating options:

1. An updated review that is defined by no new or revised recommendations and that is submitted to the *Journal of Clinical Oncology* (JCO) as a brief report. Prior to publication, the report is reviewed and approved by the leadership of the ASCO Clinical Practice Guidelines Committee (CPGC).
2. A quick, focused e-update that includes new and/or revised recommendations is posted on the guideline Wiki that is followed by a rapid JCO print update (the proposed “expedited, focused update” that is approved by a subset of the CPGC).
3. A more traditional and comprehensive ASCO guideline update that is defined by new and/or revised recommendations and is published in the JCO following conventional CPGC review and approval.

Step 4: Labeling the guideline status.

Staff will label the resulting update on the Wiki site using the following designations: archived, current, update in progress.

Systematic Literature Review

ASCO guidelines are based on systematic reviews of the literature. A protocol for each systematic review defines parameters for a targeted literature search. Additional parameters include relevant study designs, literature sources, types of reports, and pre-specified inclusion and exclusion criteria for literature identified. The protocol for this guideline was reviewed and approved by the ASCO Clinical Practice Guidelines Committee’s Breast Cancer Cancer Guideline Advisory Group.

Literature Search Strategy

PubMed and the Cochrane Collaboration Library electronic databases (\pm meeting abstracts) were searched for evidence reporting on outcomes of interest. Further details on the search strategy and results are provided in Data Supplements 3 and 4.

Data Extraction

Literature search results were reviewed and deemed appropriate for full text review by two ASCO staff reviewers in consultation with the Expert Panel Co-Chairs. Data were extracted by two staff reviewers and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the Co-Chairs if necessary. Evidence tables are provided in the manuscript and/or in Data Supplements 1 and 2.

2. DEVELOPMENT OF RECOMMENDATIONS

The guideline recommendations were crafted, in part, using the GuideLines Into DEcision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software™. This method helps Guideline Expert Panels systematically develop clear, translatable, and implementable recommendations using natural language, based on the evidence and assessment of its quality to increase usability for end users. The process incorporates distilling the actions involved, identifying who will carry them out, to whom, under what circumstances, and clarifying if and how end users can carry out the actions consistently. This process helps the Expert Panel focus the discussion, avoid using unnecessary and/or ambiguous language, and clearly state its intentions.

BRIDGE-Wiz Steps with Examples

Step #	Step
1	Choose action type Example: Prescribe
2	Based on the action type, select verb Example: Administer AND use
3	Administer and use what? (verb object) [n.b., users can add more than one verb and object(s). The verb “consider” is disallowed.] Example: administer combination of two cytotoxic drugs AND use platinum combinations
4	Check if the actions are specific and unambiguously written (Executability) Example: Modify if necessary
5	Define When (under what conditions) Example: Patients who not previously been treated for metastatic NSCLC
6	Add other conditions with AND or OR Example: AND Have ECOG PS 0 or 1 AND do not have contraindications to platinum agents
7	Check if users will be able to consistently the circumstances (Decidability) – modify if needed Example: Add language if necessary, e.g. list contraindications
8	Enter potential benefits for each Action (<i>What are the anticipated benefits of administering two cytotoxic drugs IF patients have not been previously treated for metastatic NSCLC AND don’t have contraindications to platinum drugs</i>) Example: improvement in radiologic response rate, improvement in overall survival

9	<p>Enter potential risks, harms and costs for each Action (<i>What are the anticipated risks, harms and costs of administering two cytotoxic drugs IF patients have not been previously treated for metastatic NSCLC AND Have ECOG PS 0 or 1 AND don't have contraindications to platinum drugs</i>)</p> <p>Example: List toxicities</p>		
10	<p>Judge benefit-harms balance (Options: Equilibrium, Preponderance of Risks, Harms, Costs, Preponderance of Benefits)</p> <p>Example: Preponderance of Benefits</p>		
11	<table border="1" style="width: 100%;"> <tr> <td data-bbox="285 527 1138 617">Select Aggregate Evidence Quality (High, Intermediate, Low, or Insufficient)</td> <td data-bbox="1138 527 1421 617">High</td> </tr> </table>	Select Aggregate Evidence Quality (High, Intermediate, Low, or Insufficient)	High
Select Aggregate Evidence Quality (High, Intermediate, Low, or Insufficient)	High		
12	<p>BRIDGE-Wiz proposes recommendation strength (options: Strong, Moderate, Weak) and term for the level of obligation (options: Must, Should, May)</p> <p>Example 1: Based on the Quality of Evidence High AND Preponderance of Benefit this key action statement can have a Recommendation Strength of Strong.</p> <p>Example 2: Based on this, the level of obligation should be Must or Should (choose one): Should</p>		
13	<table border="1" style="width: 100%;"> <tr> <td data-bbox="285 863 1138 911">Define who</td> <td data-bbox="1138 863 1421 911">Oncology clinicians</td> </tr> </table>	Define who	Oncology clinicians
Define who	Oncology clinicians		
14	<p>Choose a recommendation style from 4 options (n.b., can edit)</p> <p>Example: If patients have not received treatment yet for metastatic NSCLC AND have an ECOG PS 0 or 1</p> <p>Then</p> <p>Oncology clinicians should administer combination of two cytotoxic drugs (Evidence quality: High; Recommendation strength: Strong) AND oncologists should use platinum combinations, except if patients have contraindications. (Evidence quality: High; Recommendation strength: Strong)</p>		
15	<p>BRIDGE-Wiz generates an Evidence Profile, includes "Key Action Statement," "Aggregate Evidence Quality," "Benefits," "Risk, Harm, Cost," and "Benefit-Harm Assessment" for each "Action" and places to insert "Value Judgments," "Intentional Vagueness," "Role of Patient Preferences," "Exclusions", and "Notes"</p>		

Study Quality Assessment

Study quality was formally assessed for the studies identified. Design aspects related to the individual study quality were assessed by one reviewer and included factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc. The risk of bias is assessed as “low,” “intermediate,” or “high” for most of the identified evidence.

Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Expert Panel may choose to provide a rating for the strength of the recommendation (ie, “strong,” “moderate,” or “weak”). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement.
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Expert Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Expert Panel may choose to provide a rating for the strength of the recommendation (ie, “strong,” “moderate,” or “weak”).
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Expert Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Guide for Rating Quality of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits v harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Guide for Rating of Potential for Bias

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
Low risk	No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

3. OVERVIEW OF THE GUIDELINE ENDORSEMENT PROCESS

In 2006, the ASCO Board of Directors approved a policy and a set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations. The goal of the endorsement policy is to increase the number of high-quality, ASCO-vetted guidelines available to the ASCO members. Endorsement of guidelines will be considered in selected circumstances, either upon request from related professional organizations at the discretion of the CPGC, or when ASCO seeks to endorse another organization's guideline in lieu of undertaking its own guideline on the same topic. Of note, guidelines considered for endorsement by ASCO are typically developed from established guideline development groups and are based on systematic reviews of the literature.

The guideline under endorsement consideration is reviewed and approved by the ASCO CPGC. The CPGC review includes two parts: content review and methodological review. The content review is completed by an ASCO Expert Panel (Figure 3: ASCO Guideline Endorsement Content Review Form). The Expert Panel assesses the perceived clarity and clinical utility of the recommendations, and the degree to which the recommendations are consistent with the content reviewers' interpretation of the available data on the topic in question. This form was adapted by ASCO from the Cancer Care Ontario Program in Evidence-based Care Practitioner Feedback instrument. The methodological review is completed by a member of the CPGC's Methodology Subcommittee and/or by ASCO guidelines staff using the Rigour of Development subscale of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (www.agreetrust.org). The Rigour subscale consists of seven items that assess the quality of the processes used to gather and synthesize the relevant data, and the methods used to formulate the guideline recommendations (Figure 4: Rigour of Development Subscale of the Appraisal of Guidelines for Research and Evaluation II Instrument). In addition to this methodological review, ASCO staff conducts literature searches to identify relevant studies and additional systematic reviews, meta-analyses, and guidelines that have been published since the guideline under endorsement was completed. Final review and approval is completed by the ASCO CPGC after approval by the ASCO Expert Panel.

4. OVERVIEW OF THE GUIDELINE ADAPTATION PROCESS

ASCO's adapted guidelines are informed by the ADAPTE methodology (the ADAPTE process: Resource toolkit for guideline adaptation, version 2.0.; <http://www.g-i-n.net>). The objective of the ADAPTE process (<http://www.adapte.org/>) is to take advantage of existing guidelines in order to enhance efficient production, reduce duplication, and promote the local uptake of quality guideline recommendations. ASCO's adaptation process begins with a literature search to identify candidate guidelines for adaptation.

Adapted guideline manuscripts are reviewed and approved by the ASCO Clinical Practice Guidelines Committee (CPGC). The review includes two parts: methodological review and content review. The methodological review is completed by a member of the CPGC's Methodology Subcommittee and/or by ASCO guidelines staff using the Rigour of Development subscale of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (Figure 4). The Rigour subscale consists of seven items that assess the quality of the processes used to gather and synthesize the relevant data, and the methods used to formulate the guideline recommendations. In addition to this methodological review, ASCO staff conducts literature searches to identify relevant studies and additional systematic reviews, meta-analyses, and guidelines that have been published since the guideline being adapted was completed.

The content review is completed by an Expert Panel convened by ASCO that includes multidisciplinary representation. The Expert Panel members are asked to complete an eight item Guideline Endorsement Content Review Form (Figure 3) that assesses the perceived clarity and clinical utility of the recommendations, and the degree to which the recommendations are consistent with the content reviewers' interpretation of the available data on the topic in question. This form was adapted by ASCO from the Cancer Care Ontario Program in Evidence-based Care Practitioner Feedback instrument.

The Expert Panel is led by two Co-Chairs who have the primary responsibility for the development and timely completion of the guideline adaptation. Recommendations from the source guidelines are extracted into a summary matrix. Final review and approval are completed by the ASCO CPGC after approval by the ASCO Expert Panel.

As mentioned, the adaptation process starts with a literature search to identify candidate guidelines for adaptation on a given topic. A systematic search of clinical practice guideline databases, guideline developer Web sites, and the published health literature is conducted to identify clinical practice guidelines, systematic reviews, meta-analyses, and other guidance documents addressing [...add topic area(s)]. The literature search includes MEDLINE and EMBASE databases, and the Cochrane Library. To identify guidelines not indexed in medical databases, an environmental scan is undertaken of guideline databases. Finally, Web sites of organizations developing guidelines and medical specialty websites were searched and a Google™ search was undertaken to ensure that no guidelines were missed.

The guideline searches use combinations of the following search terms: [add search terms]. Guidelines and reviews are excluded if they were published before [date] and if they were written in a language other than English. Guidelines and reviews based on a clearly described systematic literature search are preferred; however, expert consensus guidance was also included for consideration. Narrative reviews and abstracts are excluded.

5. OVERVIEW OF THE PROVISIONAL CLINICAL OPINION (PCO) PROCESS

The ASCO Clinical Practice Guidelines Committee (CPGC) leadership is responsible for accepting, reviewing, and approving proposed PCO topics on behalf of the ASCO Board of Directors. The selection of a PCO topic is guided by the Topic Selection Algorithm that is used by the CPGC to guide selection of topics for ASCO's clinical practice guidelines (www.asco.org/guidelines/manual).

PCO's are informed by expeditious methodological assessments of the data in question or by using an existing systematic review conducted by an entity that produces evidence-based guidelines.

The PCO Expert Panel includes approximately six content experts and a patient representative. The membership of the Expert Panel is chosen in accordance with ASCO's Conflicts of Interest Policy Implementation for Clinical Practice Guidelines. The COI Policy calls for the majority of Expert Panel members to have no relationships with companies potentially affected by the PCO, and generally require Expert Panel co-chairs to be free from relationships with affected companies.

The PCO is approved by a unanimous vote of (1) the PCO Expert Panel members; (2) the CPGC leadership (Past-Chair, Chair, Chair-Elect, and ASCO Board Liaison) and selected content experts drawn from the CPGC membership and/or selected content experts appointed at the discretion of the CPGC Chair.

**Figure 1: Sample Expert Content Review Matrix for Guideline Updating Assessment
(adapted from the 2013 AHRQ report, Surveillance and Identification of
Signals for Updating Systematic Reviews: Implementation and Early Experience²)**

Recommendation from ASCO Guideline	Is this recommendation almost certainly still supported by the evidence?	Has there been new evidence that may change the recommendation?	Do not know
Clinical Question 1:			
Recommendation:	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
Clinical Question 2:			
Recommendation:	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

**Figure 2: Sample Summary Table for ASCO Guideline Updating Needs Assessment
(adapted from the 2013 AHRQ report, Surveillance and Identification of Signals for Updating Systematic Reviews: Implementation and Early Experience²)**

Conclusions from ASCO Guideline	Literature search yield	FDA Surveillance Alert	Expert opinion assessment	Conclusions from ASCO Expert Panel Co-Chairs
Clinical Question 1:				
Recommendation:				
Clinical Question 2:				
Recommendation:				

Figure 3: ASCO Guideline Endorsement Content Review Form

American Society of Clinical Oncology
Practice Guideline Endorsement Content Review Form*

Guideline Title: _____

Organization: _____

Reviewer Name: _____

Background and Instructions. ASCO considers clinical practice guidelines developed by other professional organizations for endorsement. This is done by ASCO most often in lieu of undertaking its own guideline on the same topic. You have been asked to provide a content review of a guideline that is under consideration for endorsement by ASCO. Please check the box that best applies for each of the following items.

	Strongly Agree	Agree	Neither Agree or Disagree	Disagree	Strongly Disagree	Unsure
The results of the studies described in this guideline are interpreted according to my understanding of the data.	?	?	?	?	?	?
The recommendations in this report are clear.	?	?	?	?	?	?
I agree with the recommendations as stated in the guideline.	?	?	?	?	?	?
The recommendations are suitable for the patients for whom they are intended.	?	?	?	?	?	?
The recommendations are too rigid to apply to individual patients.	?	?	?	?	?	?
When applied, the recommendations will produce more benefits for patients than harms.	?	?	?	?	?	?
The guideline presents options that will be acceptable to patients.	?	?	?	?	?	?
The guideline should be endorsed by ASCO.	?	?	?	?	?	?

* This form was adapted from the Cancer Care Ontario Program in Evidence-Based Care Practitioner Feedback instrument.

Figure 4: Rigour of Development Subscale of the Appraisal of Guidelines for Research and Evaluation II Instrument

Rigour of Development Subscale Item

Systematic methods were used to search for evidence.

The criteria for selecting the evidence are clearly described.

The strengths and limitations of the body of evidence are clearly described.

The methods used for formulating the recommendations are clearly described.

The health benefits, side effects, and risks have been considered in formulating the recommendations.

There is an explicit link between the recommendations and the supporting evidence.

The guideline has been externally reviewed by experts prior to its publication.

A procedure for updating the guideline is provided.

NOTE: Each subscale item is rated on a seven-point scale from 1 (strongly disagree) to 7 (strongly agree). The score for the Rigour of Development domain is calculated by summing the scores across individual items in the domain and across all raters, subtracting the lowest possible score for that domain (1 x No. items x No. of raters), then standardizing the total score as a proportion of the maximum possible score (7 x No. of items x No. of raters) minus the lowest possible score

References

1. Shiffman RN, Michel G, Rosenfeld RM, et al: Building better guidelines with BRIDGE-Wiz: development and evaluation of a software assistant to promote clarity, transparency, and implementability. *J Am Med Inform Assoc* 19:94-101, 2012
2. 3. Newberry SJ, Ahmadzai N, Motala A, et al: *Surveillance and Identification of Signals for Updating Systematic Reviews: Implementation and Early Experience*. Rockville MD, 2013