Comparative Effectiveness Review Disposition of Comments Report

Research Title: Breast Reconstruction After Mastectomy: A Systematic Review and Meta-Analysis

Draft report available for public comment from March 22, 2021, to April 21, 2021.

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Comments to Draft Report

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Comments on draft reports and the authors' responses to the comments are posted for public viewing on the website approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commenter, if this information is provided. Commenters are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Summary of Peer Reviewer Comments and Author Response

This research review underwent peer review before the draft report was posted for public comment on the Effective Health Care (EHC) website. Peer review comments and responses are summarized here.

- Reviewers found the review "*well written and the language is appropriate/clear for non-surgeons*" and that the "*report describes the results of the analysis clearly.*" Reviewers noted that the authors are "*appropriately cautious regarding the findings*." Reviewers also noted that the Implications for Future Research section was "*clear and easily translated into new research and new research needs*."
- Reviewers asked for specific clarifications, for example, (1) why studies of women undergoing breast reconstruction for prophylactic purposes were included in the review; (2) considerations that are usually made by surgeons and patients regarding timing of implant-based and autologous reconstruction with regard to chemotherapy and radiation therapy; (3) that autologous reconstruction with latissimus dorsi flaps often necessitates the use of implants; (4) how timing of radiation therapy with respect to the tissue expander versus the implant was handled in the review; and (5) how risk of bias contributed to strength of evidence assessments. The Evidence-based Practice Center (EPC) authors clarified various sections of the report in response to these comments.
- Reviewers also suggested providing details regarding how studies defined specific outcomes, such as wound dehiscence, delayed healing, scarring, implant failure, and hematoma. The EPC authors clarified these where applicable and/or noted that these definitions were provided in specific tables cited in the report.
- Reviewers did not identify any studies that were missed by our search and screening processes. Some were suggested for inclusion, but the EPC authors responded that those studies did not fulfill our a priori eligibility criteria. One study published subsequent to our draft report search date (February 14, 2020) was subsequently included in our final search (March 23, 2021).
- Reviewers made some specific suggestions regarding arm names and outcome time-points that were incorrectly extracted for some studies. The EPC authors made these corrections.
- Reviewers also suggested additions to the *Discussion* section, such as the paucity of studies in women undergoing reconstruction for prophylactic purposes. The EPC authors added those details to the *Discussion*.

Commenter & Affiliation	Section	Comment	Response
Breast Implant Working Group	General	The AHRQ draft report states that it evaluates different breast reconstruction options for women either after mastectomy for breast cancer or as breast cancer prophylaxis, so that patients, clinicians, health system leaders, and policy makers can make "well-informed decisions and thereby improve the quality of healthcare services." Our comments are aimed at helping you accomplish those goals.	We thank the reviewers from the Breast Implant Working Group for their comments. We have responded to the comments.
National Center for Health Research	Evidence Summary	This draft report states that it evaluates different breast reconstruction options for women either after mastectomy for breast cancer or as breast cancer prophylaxis, so that patients, clinicians, health system leaders, and policy makers can make "well-informed decisions and thereby improve the quality of healthcare services." Based on our work with thousands of breast cancer patients, however, we must conclude that this review does not provide answers to important questions that are necessary to succeed in those worthy goals. We have identified a number of shortcomings of the report, which we urge you to address before the report is finalized.	We thank the reviewers from the National Center for Health Research for their comments. We have responded to the comments.

Commenter & Affiliation	Section	Comment	Response
Breast Implant Working Group	General	For example, the report barely mentions prophylactic mastectomies, and BRCA mutations are not mentioned at all, despite being the major reason why women undergo prophylactic mastectomies. For those reasons, we urge AHRQ to remove the statement that this review is relevant for women who underwent prophylactic mastectomies and that it provides guidance to their healthcare providers on that topic.	We have added clarification to the *Background* and *Discussion* sections that women with BRCA1 and BRCA2 mutations are considered at high risk for breast cancer and are generally offered mastectomy as prophylaxis. As we note in the *Applicability* section of the *Discussion*, the bulk of the evidence identified in this systematic review addressed breast reconstruction after therapeutic (not prophylactic) mastectomy.
Breast Implant Working Group	General	In general, negative outcomes of reconstructive procedures are not adequately discussed in the report. For example, the discussion of the risks of reconstruction with breast implants barely mentions breast implant associated anaplastic large cell lymphoma (BIA-ALCL). Despite the length of the report and the potential lethality of BIA-ALCL, that lymphoma, which is caused by breast implants, is only mentioned 4 times; twice on page 19, once in Figure 2, and briefly on page 88. BIA-ALCL was not mentioned as a risk in the section of the report comparing different types of implants.	BIA-ALCL was not reported by the studies included in the review. Given the rarity of the cancer, this was not unexpected. We discussed BIA-ALCL in the *Background* (as a potential harm), in the *Methods* (as an outcome of interest), and in the *Findings in Relation to the Decisional Dilemmas* section of the *Discussion*. In that part of the *Discussion*, we emphasized our finding: "*Studies eligible for this SR did not address the risk of new neoplasms, in particular implant-associated anaplastic large cell lymphoma (BIA-ALCL).*"

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Breast Implant Working Group	General	In general, the lack of discussion of complications and serious health consequences from reconstruction could mislead healthcare providers who rely on this report for information about the safety of these procedures. For example, when discussing the risks of reconstruction with breast implants, the draft only mentions breast implant associated anaplastic large cell lymphoma (BIA-ALCL) 4 times: twice on page 19, once in Figure 2 (on page 6), and briefly on page 88. BIA-ALCL was not mentioned as a risk in the section of the report comparing different types of implants. The report states that the studies eligible for the review did not address the risk of neoplasms, particularly BIA-ALCL, but that is not adequate justification for almost ignoring a potentially fatal adverse event.	The harms of interest were not ignored. BIA-ALCL was not reported by the studies included in the review. Given the rarity of the cancer, this was not unexpected. We discussed BIA-ALCL in the *Background* (as a potential harm), in the *Methods* (as an outcome of interest), and in the *Findings in Relation to the Decisional Dilemmas* section of the *Discussion*. In that part of the *Discussion*, we emphasized our finding: "*Studies eligible for this SR did not address the risk of new neoplasms, in particular implant-associated anaplastic large cell lymphoma (BIA-ALCL)*." Additionally, the tables that summarize the overall evidence (Table A in the *Evidence Summary* and Table 32 in the *Discussion*) specify that no data regarding BIA-ALCL were reported.

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National Center for Health Research	General	First, the report assumes that the only kind of reconstruction after a mastectomy is to replace the breasts. It includes no discussion of the choice made by many women to "go flat" with cosmetic surgery to make the flat chest look as attractive as possible. This is important, since research has shown that 44% women did not have reconstructive surgery to replace their breast(s) after their mastectomy.[1] This oversight should be addressed because the current draft of the report makes breast reconstruction seem inevitable, which patients tell us makes it difficult to convince healthcare providers that they do not want breast reconstruction.	We have added clarification to the *Background* section that some women choose to avoid reconstructive surgery. The scope of this systematic review addresses the choice of reconstructive surgery procedures and *not* the choice of whether or not to undergo reconstruction. We have clarified this in the *Purpose of the Review subsection* of the *Introduction*.
National Center for Health Research	General	It is also essential to include the information that mastectomies for women with very early stage breast cancer are much more common i n the U.S. than any other country. Although the data are clear that women with early-stage breast cancer who undergo lumpectomy live as long as women who undergo mastectomies, the report fails to mention that when mastectomies are unnecessary, choosing lumpectomy will make reconstruction (with its risks) also unnecessary.	The choice of lumpectomy versus mastectomy is beyond the scope of the current systematic review. As stated in the Title, *Background*, *Purpose of the Review*, and in various other locations of the report, this SR is focused on breast reconstruction after mastectomy.
Breast Implant Working Group	Introduction	And, BIA-ALCL is described in the report as "an extremely rare" type of cancer, which is misleading given that the most recent data indicates it occurred in one of every 354 mastectomy patients reconstructed with textured implants, according to a study conducted at Memorial Sloan Kettering Cancer Center [1].	We have removed the word "extremely" from that sentence of the *Background*.

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Breast Implant Working Group	Introduction	The report never mentions “Breast Implant Illness;” the “systemic symptoms” that are usually referred to as “Breast Implant Illness” were only mentioned twice (page 19). Those citations do not mention well-designed published studies indicating statistically significant increases in symptoms or related diseases, such as those conducted by Watad et al. in 2018 [2] or Wee et al. in 2020[3].	Breast implant illness was not an *a priori* outcome of interest in our Protocol (based on discussions with the Key Informants and Technical Expert Panel). The symptoms of interest were pain and touch sensitivity. We also included a range of other patient-reported outcomes, such as quality of life, physical well-being, sexual well-being, and patient satisfaction, were of interest. We excluded the Watad 2018 study because no data were extractable specifically for patients with breast cancer. The Wee 2020 study only included patients who had undergone breast augmentation (not reconstruction).

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National Center for Health Research	Introduction	The report barely mentions the autoimmune, connective tissue, and neurological risks associated with breast implants, known as "Breast Implant Illness." Although the report gives passing mention of "systemic symptoms" twice on page 19, there is no discussion of well-designed, published studies that reported statistically significant increases in these symptoms or any mention of the term Breast Implant Illness. In 2019, the FDA held a 2-day meeting focused primarily on breast implant illness, and researchers have reported statistically significant increases in these symptoms and related diseases [for example, see 3,4]. Moreover, a 2020 study examining 750 patients who were diagnosed with symptoms of breast implant illness found that after their breast implants were carefully removed, symptoms such as joint and/or muscle pain, loss of hair, memory loss/cognitive problems, chronic fatigue, breast pain, persistent skin inflammation, food intolerance, and difficulty breathing disappeared or improved significantly.[5]	Breast implant illness was not an *a priori* outcome of interest in our Protocol (based on discussions with the Key Informants and Technical Expert Panel). The symptoms of interest were pain and touch sensitivity. We also included a range of other patient-reported outcomes, such as quality of life, physical well-being, sexual well-being, and patient satisfaction, were of interest. We excluded the Watad 2018 study because no data were extractable specifically for patients with breast cancer. The Wee 2020 study only included patients who had undergone breast augmentation (not reconstruction).
Breast Implant Working Group	Introduction	Instead, the mention of systemic illness in the draft report is misleading. It states "These risks of systemic symptoms and BIA-ALCL led the U.S. Food and Drug Administration (FDA) to request a recall of one manufacturer's textured implant and tissue expander in 201915 and to recommend a boxed warning for all breast implants in 2020." While the systemic symptoms were a major reason for the FDA meeting, those symptoms are unrelated to BIA-ALCL, which was the reason for the recall of one type of textured implants.	We have made this correction by removing reference to the systemic symptoms in that sentence about the FDA recall.

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National Center for Health Research	Introduction	Furthermore, the mention of these systemic symptoms appears to be conflated with discussion of BIA-ALCL on page 19, when it states "These risks of systemic symptoms and BIA-ALCL led the U.S. Food and Drug Administration (FDA) to request a recall of one manufacturer's textured implant and tissue expander in 2019 and to recommend a boxed warning for all breast implants in 2020." The recall was due to BIA-ALCL, not to Breast Implant Illness symptoms.	We have made this correction by removing reference to the systemic symptoms in that sentence about the FDA recall.
National Center for Health Research	Introduction	The draft report notes that it also evaluates breast reconstruction options for those women who had prophylactic mastectomies, but the report barely mentions this, merely stating that more women who have undergone prophylactic mastectomies need to be enrolled in clinical studies. Unfortunately, the report lacks information that is relevant for the diverse groups of women who undergo prophylactic mastectomies. Additionally, BRCA mutations are not mentioned in the report, despite being a key factor that influences women's decision to undergo prophylactic mastectomies. We therefore strongly urge AHRQ to remove the statement that this review is relevant for women who had mastectomies as breast cancer prophylaxis and that it provides guidance to healthcare providers on this issue.	We have added clarification to the *Background* and the *Discussion* sections that women with BRCA1 and BRCA2 mutations are at high risk for breast cancer and are generally offered mastectomy as prophylaxis. As we note in the *Applicability* section of the *Discussion*, the bulk of the evidence identified in this systematic review addressed breast reconstruction after therapeutic (not prophylactic) mastectomy. However, we do not believe that the sparsity of evidence regarding women who undergo breast reconstruction for prophylactic purposes makes the review irrelevant for the prophylactic context. The sparsity of evidence is important to point out and should be considered in decisionmaking for this important subpopulation of women.

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National Center for Health Research	Methods	There is also limited information in the report regarding outcomes of importance to patients. The report lists surgical complications as well as patient satisfaction with aesthetic results and psychosocial well-being after only 2 years, but the report does not describe whether patient satisfaction was reported anonymously or to the surgeons; the latter would clearly bias the results.	We involved patient stakeholders as Key Informants in the project. The full set of outcomes of interest for the review is intended to be relevant to patients, providers, and other decisionmakers. Most studies reporting patient satisfaction data used the Breast Questionnaire (BREAST-Q), a validated and standard instrument that is self-reported by patients. The included studies generally did not report information regarding who collected the data. We have added this as a potential limitation in the *Discussion* section.
National Center for Health Research	Discussion and Conclusions	In addition, the report does not explain that there is no scientifically solid data on long-term (long er than 10 years) complication rates comparing different types of implant-based reconstruction (IBR). Since breast reconstruction is intended to last for decades, this limits how informative the report actually is.	We have added the sparsity of long-term outcome data as a limitation in the *Strengths and Limitations of the Evidence Base* section of the *Discussion*.
National Center for Health Research	Discussion and Conclusions	Finally, it is stated in the report that the conclusions apply generally to mostly White, middle-aged, non-obese women in high-income countries who are being treated for breast cancer, which raises questions about how generalizable the report is to all women considering mastectomy and reconstruction. That shortcoming should be explicitly acknowledged.	The *Applicability* section of the *Discussion* states this point. The next sentence adds: *"It is unclear to what extent the findings of this SR are broadly applicable beyond these populations."*