Peer Review File
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Reviewer A

This is a lovely editorial piece that encapsulates the topic and the issues.

Reply: Thank you very much for your kind comments.

Reviewer B

This is a comment on an interim report of an RCT investigating the innervation of DIEP flaps. The commentary could benefit from a better focus; please see the specific comments.

Reply: Thank you for your comments. Please see below in red for the authors' point-by-point responses. We hope that these revisions improve the paper such that you and the reviewers now deem it worthy of publication.

• Some of the statements in the first paragraph are a bit unscientific. For example, "
while patients with non-innervated flaps experience significant decrease in their quality of life due to significant reduction in sensation.". Compared to what? What type of quality of life? That patients who have had an innervated flap score higher on sensation than those who have not does not itself imply that the patients have a decreased quality of life? If we are talking about general quality of life or even general breast-related quality of life, how do you know that sensation is the causal factor? The same goes for that sensation per se restores ' a patient's sense of self'. Please clarify exactly what has been studied and how and what that demonstrates.

Reply: Thank you very much for your comments. As the reviewer recommends, we have clarified the statements on improved sensation and quality of life in breast reconstruction (page 1, paragraph 1). Decreased sensation can lead to inadvertent injury, and recovery of sensation can contribute to body image and help patients feel that their reconstructed breasts are a part of themselves. Though these effects have not be quantitatively studied in a validated PROM made specifically for sensation after breast reconstruction, they should intuitively be beneficial for patients and contribute to improved quality of life. There are also a few studies which have subjectively looked at reconstructed breast sensation and quality of life which are referenced in the article. Therefore, we also expand upon the point that quantitatively measured improvements in sensation may not translate directly to improved quality of life in page 1, paragraph 3 and page 2, paragraph 3.

• Please consider rewriting the second paragraph (lines 24-34) to focus on the main findings and not the individual reviews/studies, as this is often easier for a reader to follow.

Reply: Thank you for the suggestion. As recommended, the second paragraph has been rewritten for easier readability (page 1, paragraph 2).

• Some of the sentences in the manuscript are so long that they have to be read several times for the reader to grasp the meaning. For example, "Although these recent systematic reviews demonstrate there is improvement in sensation with flap neurotization, it is challenging to interpret the current literature on breast flap neurotization due to heterogeneity of neurotization

techniques, use of autograft, allograft, or nerve conduits, different protocols for objective measurements of sensory recovery, and variations in other potentially confounding factors such as breast and flap size, bilateral versus unilateral reconstruction, prophylactic versus therapeutic mastectomies, timing of reconstruction, adjuvant chemotherapy and radiation therapy, and length of follow up time" Please consider making the information a bit more easily digestible for the reader.

Reply: Thank you for the suggestion. As recommended, this sentence has been rewritten and expanded for easier readability (page 1, paragraph 3).

• The statement "These limitations, coupled with some evidence of spontaneous flap reinnervation19-22, have forestalled the widespread adoption of autologous breast reinnervation." It seems to be a speculation on why more flaps are not innervated. Please clarify that this is the authors' interpretation and not a fact.

Reply: Thank you for the comments. We have tried to clarify this statement by expanding upon the current limitations in understanding the benefits of breast flap innervation, as well as potential downsides (page 2, paragraph 3). We hope this helps to explain why breast flap neurotization is a topic of growing interest, but has not yet been widely adopted in most centers.

• As this is a comment on a study, is it necessary to give a summary of it? For example, the following paragraph is not a comment on the results but merely a summary of the study:

"Therefore, Bubberman et al sought to address the shortcomings in the current 50 literature by designing one of the first randomized controlled trials (RCTs) investigating sensory recovery of innervated DIEP flaps23. This article presents their preliminary results of a single center, multi surgeon RCT using a standardized neurotization technique with direct coaptation of the second or third intercostal nerve to the sensory intercostal nerve in the DIEP flap with 9-0 nylon suture and fibrin sealant. Sensory testing of tactile touch and 55 temperature was tested pre-operatively and at 3, 6, 12, 18, and 24 month follow up using 56 SWM, PSSD, and thermostimulator. There were 19 patients and 29 breasts included in the 57 innervated group, and 22 patients and 38 breasts included in the non-innervated group. The 58 authors reported 6 failed coaptations; 3 due to insufficient nerve length, 2 due to no recipient nerve found, and 1 that was sacrificed during a flap re-exploration."

Is the article not meant to be read together with the commented study?

Reply: Thank you for the comments. We have significantly shortened this paragraph to condense the results of the Bubberman et al study (page 1, paragraph 4). While we agree that this article is meant to be read together with the commented study, we believe a short summary highlighting the methodology and results would be helpful for the readers as a reminder. By highlighting the importance of neurotization technique and quantitative measurements of sensation in this short summary, we hoped to draw reader's attention to the context of the heterogeneity of current literature, which is described in this article. The results are also important to include, as they are compared with the outcomes in the current literature in this article.

• One of the last points of the manuscript is very important: “However, it remains to be determined whether the changes in sensation as measured in objective testing translate to 103 clinically significant improvements in protective, tactile, and erogenous sensation, and thus improvement in patient-reported outcomes.” Could you please clarify if you believe the current RCT will be able to answer these questions? Do we know what a clinically relevant difference in BREAST-Q is, for example?

Reply: Thank you for the comments. While the BREAST-Q is not a PROM specifically designed for sensation in breast reconstruction, it has a validated module related to breast sensation and is currently the most validated and utilized PROM for breast. A minimal important difference score of 4 points has been proposed to be clinically relevant (Voineskos SH, Klassen AF, Cano SJ, Pusic AL, Gibbons CJ. Giving Meaning to Differences in BREAST-Q Scores: Minimal Important Difference for Breast Reconstruction Patients. Plast Reconstr Surg. 2020 Jan;145(1):11e-20e). We have included these points in the article (page 2, paragraph 3).

• Nothing is mentioned in the manuscripts about any downsides of innervating DIEP-flaps. Please add a comment on this. If there were no downsides, it would have become standard practice many years ago, albeit the scientific evidence is low?

Reply: Thank you very much for your suggestion. As the reviewer recommends, we have added a comment about the potential downsides of breast flap neurotization (page 1, paragraph 3). Please refer to the response to question 3 for more information.