American Association of Tissue Banks® AATB TPG, LLC

April 7, 2021

Janet Woodcock, MD
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

In Re: FDA Safety Communication on March 31, 2021 titled *Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates*

Submitted electronically at Janet.Woodcock@fda.hhs.gov

Dear Dr. Woodcock:

The American Association of Tissue Banks (AATB or Association) and the American Association of Tissue Bank's Tissue Policy Group, LLC (AATB TPG) submit these comments related to a safety communication on March 31, 2021 by the Food and Drug Administration (FDA or Agency) titled *Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates.* In reviewing the communication, not only are we concerned that the information presented lacks scientific rigor by not including a comprehensive evaluation of all ADM data, while also not detailing the full limitations of the dataset FDA reviewed, but we also caution that the information presented does a disservice to women – those who are considering, or who have undergone, breast reconstructive surgery, especially given that ADMs for implant-based breast reconstruction has become the standard of care. Especially in light of the new Administration's focus on maintaining scientific integrity, we are disappointed in this communication, as further detailed below.

The American Association of Tissue Banks (AATB) is a professional, non-profit, scientific and educational organization. It is the only national tissue banking organization in the United States, and its membership totals approximately 120 accredited tissue banks and 2,000 individual members. These banks recover tissue from more than 58,000 donors and distribute in excess of 3.3 million allografts for more than 2.5 million tissue transplants performed annually in the U.S. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

The AATB's Tissue Policy Group (TPG), LLC (AATB TPG or TPG) includes Chief Executive Officers and senior regulatory personnel from U.S. tissue banks that process donated human tissue. The purpose of the TPG is to drive public policy in furtherance of the adoption of laws and regulations that foster the safety, quality and availability of donated tissue. The TPG's membership is responsible for the vast majority of tissue available for transplantation within the U.S.

With respect to the scientific issues, we note multiple problems with the communication and the single analysis performed by the Agency, including a misleading title, focus on a single unpublished analysis, a lack of key information (including data tables and the statistical analysis and criteria employed), limited focus on certain surgical types while also (by default) comparing two different surgical techniques, lack of patient-reported outcomes (PROs), and failure to acknowledge other published studies that show disparate results. Simply put, the analysis performed by the Agency lacked the necessary scientific rigor (i.e., lacks comprehensive data inclusion and is limited to only certain surgical procedures) to be shared publicly, and, as such, **we request the FDA update the communication with additional clarifications, as noted below.**

Misleading title. The title of the communication -- *Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates*, which suggests that there is a definitive difference between ADM products, is not consistent with the actual text in which the FDA acknowledges four times that certain ADMs "may have" a higher risk profile. Therefore, the Agency should ensure that the key information shared with the public is accurately represented and consistent in messaging. Given that, ***we request, at a minimum, the title be edited to acknowledge uncertainty in whether certain ADMs may have different complication rates.***

Single, unpublished analysis and lack of data tables and other key information. The Agency acknowledges in its communication that it performed its own analysis of the data collected as part of the Mastectomy Reconstruction Outcomes Consortium (MROC). Based on the references provided, it seems as if this analysis is from 2012-2015, with a two year follow up. Unfortunately, based on the FDA's summary of its own analysis (i.e., "suggests that two ADMs . . . . may have a higher risk profile than others."), the FDA failed to provide key data tables, p-values, confidence intervals, definitions of complications, major complications and other key analytical parameters or other necessary information, which would be required for a peer-reviewed publication and allow the reader to critically review the data and analysis against the conclusions. In addition, it is unclear how relevant the data is, given advances in surgical techniques. Therefore, it is unclear why the Agency would share certain potential conclusions with the public without providing additional context, especially given the lack of peer review. Therefore, **at a minimum, *we request the FDA provide clear data tables, statistical approach, parameter definitions and other key information in an updated communication.***

Limited surgical techniques involved. The Agency notes that its analysis was limited to "immediate, two-stage, under-the-muscle, implant-based reconstruction with up to two-year follow-up" comparing to a "control group which did not receive ADM and groups receiving one of the four ADM brands." Thus, by its very nature, the FDA's analysis did not include pre-pectoral placement of ADMs for breast reconstruction, given that this technique is not "under-the-muscle".[1] Further, to create the "no ADM" versus "ADM" cohorts, the analysis would have likely relied on two different surgical techniques – (1) partial muscle coverage or sub-pectoral placement with ADM and (2) full muscle coverage without ADM. Therefore, in acknowledging the confounding factors and limited application, the Agency failed to make clear that the analysis not only focused on ADM use but, by default, the two cohorts also differed in surgical technique, which can influence the overall

[1] For more information on the pre-pectoral surgical technique and its benefits and current use, see here.

findings. Thus, ***we request, that, at a minimum, the FDA clarify in the communication that surgical techniques also vary with the use or non-use of ADMs and further note that the analysis does not take into consideration pre-pectoral placement of the breast implant.***

Lack of PROs. During the March 2019 Panel discussion, FDA officials highlighted the value of PROs, and yet, the Agency's analysis failed to include such information, even though references 1 and 2 (related to peer-reviewed analysis of the MROC data) heavily report on PROs and thus the data were clearly available for the Agency's analysis. Given that the Agency has deemed that their communication need not include PROs, we look forward to further discussing the value of PROs, when they are available, in additional research, especially in light of a sister agency's draft report[2] on this topic which notes that "[r]egarding ADMs, their use does not appear to impact patient-reported clinical outcomes."

Failure to include additional studies. In providing support for its analysis, the Agency opted to reference six previously published studies that support its analysis, but unfortunately the Agency failed to include additional studies that demonstrate results that did not support the Agency's position and are thus favorable to the safety and effectiveness of ADMs.

The Agency's approach runs afoul of guidance titled *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims*, that requires industry to "evaluate the **totality** of scientific evidence" (emphasis added). Examining the totality of the evidence is also a requirement of FDA submissions; industry is expected to include all studies, regardless of the outcome, to provide a balanced perspective on the product's performance in the submission for FDA to evaluate.

In selecting the six studies, the Agency failed on at least two levels. First, it did not provide a comprehensive analysis of the literature. And, it did not ensure that the referenced studies were the most relevant and up-to-date information. With respect to the literature analysis, the Agency also failed to be transparent by not supplying the search terms used and the rules for inclusion and exclusion of articles included in its communication that resulted in only six being chosen, given that there were 319 returns in PUBMED when searching, "ADM and breast reconstruction" -- 16 in 2021

[2] The AATB and TPG note that the draft report also states the following:
Use versus nonuse of human ADMs during IBR: The results are inconsistent regarding whether ADM use impacts physical well-being, psychosocial well-being, satisfaction with breast aesthetics, pain, or risks of wound dehiscence or capsular contracture. ADM use probably increases the risk of implant failure/loss or need for explant surgery (summary adjOR 1.28, 95% CI 0.97 to 1.70; 6 studies) (Moderate SoE) and may increase the risk of infections not explicitly related to the implants or ADM (summary adjOR 1.56, 95% CI 0.96 to 2.53; 7 studies) (Low SoE). However, ADM use and nonuse groups probably experience comparable risks of seroma (summary adjOR 1.52, 95% CI 0.62 to 3.71; 4 studies) (Moderate SoE) and unplanned repeat surgeries for revision (Moderate SoE). ADM use and nonuse groups may experience comparable risks of necrosis (summary adjOR 0.89, 95% CI 0.63 to 1.25; 4 studies) (Low SoE).
While this information, on its face, may seem to support the FDA's other conclusions, the sister agency (Agency for Healthcare Resarch and Quality or AHRQ) provided additional context related to its analysis – namely, the odds ratios and confidence intervals as well as a measure of the standard of evidence. Not only does the AATB and the TPG appreciate that scientific rigor, but we would also note that AHRQ determined that there was a low or moderate standard of evidence for those statements. Further, given that the 95% confidence intervals for the odds ratio crossed one, the values are not considered statistically significant. Finally, AHRQ provided an opportunity for full review of the data, including public comment, before finalizing the document. That transparency of key research information is important.

thus far; 80, 2020 (as of April 1, 2021); and 78, 2019. Thus, from PUBMED, there were at least 172 articles to analyze just over two years, and unfortunately the FDA only chose to cite six.

In addition, the Agency also failed to follow its own guidance titled *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry*, that states, "[c]hanges over time in the practice of medicine may affect the usefulness of some trials for contributing data to a meta-analysis. Older trials may no longer be relevant, if medical practice has changed such that current practices are able to prevent or reduce the occurrence of the safety outcome under investigation." Thus, in performing literature searches for FDA submissions, industry is typically held to the standard that references be less than 5-years old, unless they are foundational. Foundational articles must be supported with current literature. The FDA bibliography contains four articles (refereces 3-6) that are more than 5 years old (without any current literature to support them), while references 1 and 2 collect data from 2012-2015; and thus, do not adequately represent the evolution of surgical techniques and the current state of ADM safety and effectiveness in breast reconstruction. Thus, the Agency failed in its communication to follow its own guidance to ensure that the literature cited is the most relevant and up-to-date.

In light of these limitations, please note additional studies, contrary to the communication's findings, which should have been included in the Agency's analysis:

Brooke S, Mesa J, Uluer M, Michelotti B, Moyer K, Neves RI, Mackay D, Potochny J. Complications in tissue expander breast reconstruction: a comparison of AlloDerm, DermaMatrix, and FlexHD acellular inferior pole dermal slings. Ann Plast Surg. 2012 Oct;69(4):347-9. doi: 10.1097/SAP.0b013e31824b3d97. PMID:22868313. https://pubmed.ncbi.nlm.nih.gov/22868313/

Seth AK, Persing S, Connor CM, Davila A, Hirsch E, Fine NA, Kim JY. A comparative analysis of cryopreserved versus prehydrated human acellular dermal matrices in tissue expander breast reconstruction. Ann Plast Surg. 2013 Jun;70(6):632-5. doi: 10.1097/SAP.0b013e318250f0b4. PMID: 23429218. https://pubmed.ncbi.nlm.nih.gov/23429218/

Palaia DA, Arthur KS, Cahan AC, Rosenberg MH. Incidence of Seromas and Infections Using Fenestrated versus Nonfenestrated Acellular Dermal Matrix in Breast Reconstructions. Plast Reconstr Surg Glob Open. 2015 Dec 9;3(11):e569.doi: 10.1097/GOX.0000000000000559. PMID: 26893994; PMCID: PMC4727721.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4727721/

Schnarrs RH, Carman CM, Tobin C, Chase SA, Rossmeier KA. Complication Rates With Human Acellular Dermal Matrices: Retrospective Review of 211 Consecutive Breast Reconstructions. Plast Reconstr Surg Glob Open. 2016 Nov 21;4(11):e1118.doi: 10.1097/GOX.0000000000001118. PMID: 27975023; PMCID: PMC5142489. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5142489/

Lee KT, Mun GH. A Meta-analysis of Studies Comparing Outcomes of Diverse Acellular Dermal Matrices for Implant-Based Breast Reconstruction. Ann Plast Surg. 2017 Jul;79(1):115-123. doi:10.1097/SAP.0000000000001085. PMID: 28509698.https://pubmed.ncbi.nlm.nih.gov/28509698/

Chang, E. I. & Liu, J. Prospective unbiased experience with three acellular dermal matrices in breast reconstruction. Journal of surgical oncology 116, 365-370, doi:10.1002/jso.24656 (2017). https://pubmed.ncbi.nlm.nih.gov/28444764/

Sobti N, Liao EC. Surgeon-Controlled Study and Meta-Analysis Comparing FlexHD and AlloDerm in Immediate Breast Reconstruction Outcomes. Plast Reconstr Surg. 2016 Nov;138(5):959-967. doi: 10.1097/PRS.0000000000002616. PMID: 27782982. https://pubmed.ncbi.nlm.nih.gov/27782982/

Therefore, on balance, the current evidence is not strong enough to suggest a significant difference between ADMs. And, with that, it is unclear why such a communication was warranted. In light of this lack of key data, ***we request, at a minimum, that the aforementioned studies (and resultant conclusions) be added to the communication.***

Given the aforementioned limitations, the information presented by the Agency provides a disservice to the public and especially to the women who have received and are receiving breast reconstruction with ADMs, given that the information (as acknowledged by the Agency) is not definitive, does not require immediate action, seems solely designed to promote its perspective conclusions, does not promote true informed consent, and fails to acknowledge the standard of care.

Not definitive. As the Agency acknowledges multiple times within the communication, the data related to whether ADMs may vary in safey is not definitive. As such, it is unclear why the FDA felt as if the information would be beneficial for women receiving post-mastectomy implant-based reconstruction and their health care providers. This is further confounded by the fact that the communication notes that it is possible to perform implant-based reconstruction without ADMs, but it fails to note that this requires a different surgical technique and its limitations and complications lead to the use of ADMs to overcome these challenges. And, as such, the overall end result of the procedure may vary, based on the surgical technique and not the ADM itself.

No immediate action. The information acknowledges that the "FDA does not recommend reoperation or removal of implanted ADM as a preventive measure." Rather, it seems solely to be designed to create unnecessary worry among women who have received or are receiving breast reconstructive procedures.

Fails to enhance informed consent. For all of the reasons outlined above, the recent FDA information fails to enhance informed consent. As previously indicated in our comments to the draft guidance document titled *Breast Implants - Certain Labeling Recommendations to Improve Patient Communication*, the AATB and the TPG support additional informed consent related both to the overall labeling for breast implants as well as communication related to other medical products,

including ADMs, which may be used in conjuction with breast implants. The final guidance notes the following, which is better than the communication because it acknowledges that the ADM use is tied to the surgical approach and ensures that the full context is provided:

> "My physician has discussed the potential use of other implanted products during my breast implant surgery. My physician has also discussed the risks and benefits of using these implanted products and their planned surgical approach."

Therefore, for any future communication with the public and the medical community, we hope that the Agency follows its guidance document and provides a more balanced approach related to informed consent for women receiving these procedures.

Standard of care. That balanced approach is particularly important, given the current use of human ADMs for breast implant-based reconstruction. Human ADMs were first described for use in breast surgery in 2001.[3] Since that time, the vast majority of breast-implant-based reconstructions utilize human ADMs. According to the American Society of Plastic Surgeons, of the approximately 101,657 breast reconstruction procedures performed by member surgeons in 2018, about 83,200 (roughly 82%) utilized tissue expanders or breast implants. Of these procedures, approximately 74% (61,713) utilized ADMs. Recognizing human ADMs as the proven standard of care, major U.S. payers (e.g. Anthem, CIGNA, Blue Cross Blue Shield, and Aetna) currently regard the use of acellular dermal matrix with breast reconstruction as a clinically supported and clearly reimbursable use, where the tissue assists the surgeons in reconstructing the breast at the time of mastectomy in a process that improves cosmetic outcome and limits the need for further surgical procedures.[4] For more information regarding the history of its use, please see our attached ADM primer.

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We hope that you will find this information useful in your deliberations, and we look forward to future conversations, as part of the upcoming Panel meeting on the topic or as a separate discussion, if the Agency would find that helpful. As previously noted, we are discouraged, especially with this Administration's mandate, that the scientific integrity of the data analysis was not maintained in this communication, and, as such, the communication did a disservice to the American public and especially to women who have received or are receiving reconstructive surgery, especially given that ADMs for implant-based breast reconstruction has become the standard of care. As such, we recommend that the FDA appropriately update your communication to include relevant, scientific information. The AATB and the TPG stand ready and willing to assist the FDA with its deliberations in any way that you deem appropriate.

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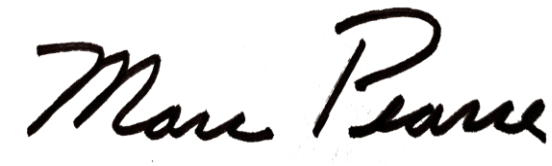
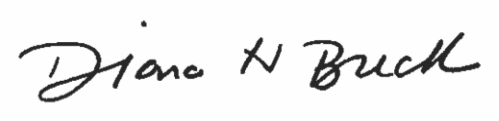
[3] Margulies I, Salzberg C. The use of acellular dermal matrix in breast reconstruction: evolution of technique over 2 decades. Gland Surgery 2019; 8(1):3-10.

[4] Sbitany, Hani, M.D.; Sandeen, Sven N., M.D.; Amalfi, Ashley N., M.D.; Davenport, Mark S., M.D.; Langstein, Howard N., M.D. *Acellular Dermis–Assisted Prosthetic Breast Reconstruction versus Complete Submuscular Coverage: A Head-to-Head Comparison of Outcomes.* Plastic and Reconstructive Surgery: December 2009 - Volume 124 - Issue 6 - p 1735-1740; doi: 10.1097/PRS.0b013e3181bf803d

Respectfully,





Marc Pearce, MBA
President & CEO
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Diana Buck
Chair
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CC: Dr. Peter Marks & Dr. Jeffrey Shuren

Attachment: ADM primer

American Association of Tissue Banks® AATB TPG, LLC

Primer: Use of Human Acellular Dermal Matrices (ADMs) in Breast Reconstruction

Introduction

The American Association of Tissue Banks (AATB) and the AATB Tissue Policy Group (TPG) strongly believe that human acellular dermal matrixes (ADMs) are appropriately regulated solely as 361 human cells, tissues, and cellular and tissue-based products (HCT/Ps) when promoted under the manufacturer's objective intent for use to reinforce, support, protect, or cover soft tissue weaknesses, including for use in breast reconstruction procedures. To further support those arguments and to provide a history of the use of skin grafting (including the use of human ADMs for breast reconstruction), the AATB has collected key scientific articles related to the history of skin grafting, the history of the use of human ADMs in breast reconstruction as well as data related to the safety and effectiveness of such products.

History of Skin Grafting

Recognizing the need to assist individuals with severe burns, skin grafting was one of the first allografts. The use of allograft skin dates back to Reverdin in 1869 describing the use of skin grafting in clinical practice for the first time.[1] George Pollock used his own skin in addition to the patient's own skin to cover a burn in 1871.[2] The first report of successful use of allograft skin to treat a burn was by Girdner in 1881.[3] In 1903, Wentscher reported that allograft skin retained cellular viability after 3-14 days.[4] James Barrett Brown, M.D. (1899-1971), with his work in the early 1930s, revolutionized the concepts of skin grafting.[5,6] His work highlighted the key nature of allografts – that split thickness skin from the mother was completely absorbed within three weeks of being transferred to her severely burned son.[7] Organizations, such as the Ancient Arabic Order of the Nobles of the Mystic Shrine – or Shriners – helped further the use of skin grafts to assist burn care to children for 50 years.[8] As skin grafting became more common to save the life of burn patients, banking of skin paralleled the development of blood banks in the 1930s and gave way to the development of The Navy Tissue Bank in 1949. One of the major contributions of the Navy Tissue Bank was the development of cryopreservation to prolong the shelf life of banked skin to make its use more widely available and retain cellular viability. To further expand the use of donated skin, decellularization

[1] Reverdin JL. Greffeepidermique, experiencefaitedans le service de M le docteurGuyon, a l'hopitalnecker. Bull Imp SocChir Paris. 1869;10:511–5

[2] Pollock GD. Cases of skin grafting and skin transplantation. Trans ClinSocLond. 1871;4:37–54

[3] Girdner JH. Skin-grafting with grafts taken from the dead subject. Med Record NY. 1881;20:119–20

[4] Wentscher J. A further contribution about the survivability of human epidermal cells. Dtsch Z Chir. 1903;70:21–44.

[5] Blair VB, Brown JB, Hamm WG. Early Cre of burs. JAMA 1932;98:1355-1359.

[6] Blair VP, Brown JB. The use and uses of split thikness skin grafts of intermediate thickness. Surg Gynocol Obstet. 1928:98:82-97.

[7] Ibid.

[8] Čapek KD, Culnan DM, Desai MH, Herndon DN. Fifty Years of Burn Care at Shriners Hospitals for Children, Galveston. Ann Plast Surg. 2018;80(3 Suppl 2):S90–S94. doi:10.1097/SAP.0000000000001376

technologies were developed and applied to the dermal layer of skin for a variety of intended uses and are the subject of this document.

Human ADMs have been used for many years in various applications, many of which address congenital abnormalities or reconstruction following trauma or disease. These include, but are not limited to, pelvic, abdominal, and chest wall reconstructions;[9] diabetic foot ulcers,[10,11,12] chronic wounds,[13] dural repair;[14] hand surgery;[15] urethral reconstruction;[16] burn surgery;[17] ENT procedures,[18] venous leg ulcers,[19,20,21] and gingival graft procedures.[22]

Use of human ADMs within breast reconstruction

Human acellular dermal matrixes (ADMs) were first described for use in breast surgery in 2001.[23] Since this initial report, ADMs have become an increasingly common component of implant-based breast reconstruction procedures.[24] According to the American Society of Plastic Surgeons, of the approximately 101,657 breast

[9] Butler CE, Langstein HN, Kronowitz SJ. Pelvic, abdominal, and chest wall reconstruction with AlloDerm in patients at increased risk for mesh-related complications. *Plast Reconstr Surg*. 2005 Oct. 116(5):1263-75; discussion 1276-7.

[10] Guo X, Mu D, Gao F. Efficacy and safety of acellular dermal matrix in diabetic foot ulcer treatment: A systematic review and meta-analysis. Int J Surg. 2017 Apr;40:1-7. doi: 10.1016/j.ijsu.2017.02.008. Epub 2017 Feb 14

[11] Cazzell S, Vayser D, Pham H, Walters J, Reyzelman A, Samsell B, Dorsch K, Moore M. A randomized clinical trial of a human acellular dermal matrix demonstrated superior healing rates for chronic diabetic foot ulcers over conventional care and an active acellular dermal matrix comparator. Wound Repair Regen. 2017 May;25(3):483-497. doi: 10.1111/wrr.12551. Epub 2017 Jun 12.

[12] Reyzelman AM, Bazarov I. Human acellular dermal wound matrix for treatment of DFU: literature review and analysis. J Wound Care. 2015 Mar;24(3):128; 129-34. doi: 10.12968/jowc.2015.24.3.128.

[13] Walters J, Cazzell S, Pham H, Vayser D, Reyzelman A. Healing Rates in a Multicenter Assessment of a Sterile, Room Temperature, Acellular Dermal Matrix Versus Conventional Care Wound Management and an Active Comparator in the Treatment of Full-Thickness Diabetic Foot Ulcers. Eplasty. 2016;16:e10. Published 2016 Feb 4.

[14] Chaplin JM, Costantino PD, Wolpoe ME, Bederson JB, Griffey ES, Zhang WX. Use of an acellular dermal allograft for dural replacement: an experimental study. *Neurosurgery*. 1999 Aug. 45(2):320-7.

[15] Kim JY, Buck DW 2nd, Kloeters O, Eo S, Jones NF. Reconstruction of a recurrent first dorsal web space defect using acellular dermis. *Hand (N Y)*. 2007 Dec. 2(4):240-4.

[16] Kim JY, Bullocks JM, Basu CB, Bienstock A, Link R, Kozovska M. Dermal composite flaps reconstructed from acellular dermis: a novel method of neourethral reconstruction. Plast Reconstr Surg. 2005 Jun. 115(7):96e-100e.

[17] Sheridan R, Choucair R, Donelan M, Lydon M, Petras L, Tompkins R. Acellular allodermis in burns surgery: 1-year results of a pilot trial. J Burn Care Rehabil. 1998 Nov-Dec. 19(6):528-30.

[18] Agir H, Eren GG, Yasar EK. Acellular Dermal Matrix Use in Cleft Palate and Palatal Fistula Repair: A Potential Benefit? J Craniofac Surg. 2015 Jul;26(5):1517-22.

[19] Cazzell S. A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers. Wounds. 2019 Mar;31(3):68-74. Epub 2019 Jan 31.

[20] Hughes, OB, Rakosi A, Macquhae F, Herskovitz I, Fox JD, Kirsner RS. A Review of Cellular and Acellular Matrix Products: Indications, Techniques, and Outcomes. Plast Reconstr Surg. 2016 Sep;138(3 Suppl):138S-47S. doi: 10.1097/PRS.0000000000002643

[21] Cazzell S. A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers. Wounds. 2019 Mar;31(3):68-74. Epub 2019 Jan 31.

[22] Aichelmann-Reidy ME, Yukna RA, Evans GH, Nasr HF, Mayer ET. Clinical evaluation of acellular allograft dermis for the treatment of human gingival recession. J Periodontol. 2001 Aug. 72(8):998-1005.

[23] Margulies I, Salzberg C. The use of acellular dermal matrix in breast reconstruction: evolution of technique over 2 decades. Gland Surgery 2019; 8(1):3-10.

[24] Sheina A Macadam, MD MHS and Peter A Lennox, MD. Acellular dermal matrices: Use in reconstructive and aesthetic breast surgery. Can J Plast Surg. 2012 Summer; 20(2): 75–89.

reconstruction procedures performed by member surgeons in 2018, about 83,200 (roughly 82%) utilized tissue expanders and/or breast implants. Of these procedures, approximately 74% (61,713) utilized ADMs. Implant-based reconstruction can be performed either as a 1-stage "direct-to-implant" procedure, if sufficient skin flap is preserved post-mastectomy, or as a 2-stage procedure. In the 2-stage approach, a tissue expander is placed at the mastectomy space, followed a few months later by replacement of the expander with the permanent implant.

Safety of human ADMS within breast reconstruction

No significant changes in complication rates. In order to assess the safety of ADMs, several studies have evaluated the outcomes of ADM usage in breast reconstruction compared to non-ADM procedures. In a retrospective review using the American College of Surgeon's (ACS) National Surgical Quality Improvement Program (NSQIP) database, Ibrahim, et al compared outcomes from all tissue expander/implant expander (TE) breast reconstruction procedures (immediate or delayed) from 2005 to 2011 with and without the use of ADM.[25] Of the 19,100 total TE procedures, 3,301 used an ADM, and found that the overall complication rates with and without ADM were not statistically significantly different. Similarly, using the same ACS NSQIP registry, Davila, et al compared complication rates of immediate TE breast reconstruction procedures performed with or without ADM between 2006 and 2010.[26] Out of 9,159 patients, 1,717 involved the use of ADM, while 7,442 without, and between the two cohorts, nearly identical complication rates were reported.

More recently, Heidemann, et al performed a systematic review of potential complications associated with the use of ADM in immediate breast reconstruction (IBR).[27] The review covered 9 independent studies, totaling 778 cases using ADM in breast reconstruction. They found that the use of ADM does not inherently change the complication rates of IBR compared to non-ADM procedures. A prospective study evaluated ADM use in immediate TE reconstruction comparing three separate cohorts – TE reconstruction without ADM (90 cases), with ADM (100 cases), or selective use based on patient criteria (260 cases).[28] Interestingly, the authors found that ADM usage was associated with lower overall complication rates, particularly when selectively used based on patient-specific criteria. Hence, adopting patient selection criteria for ADM usage is arguably the most effective way to reduce any potential complications following breast reconstruction.

Finally, a recent randomized clinical trial with a six-month follow up by Lohmander et al[29] found that IBR with ADM carried a risk of implant loss similar to IBR without ADM.

Benefits of human ADMS within breast reconstruction

The mastectomy surgery itself often results in a thin, weakened and inadequate skin envelope that requires support and protection from mechanical stress induced by the implant placed into the reconstructed breast to

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[25] Ibrahim, A.M., et al., *Analysis of the National Surgical Quality Improvement Program database in 19,100 patients undergoing implant-based breast reconstruction: complication rates with acellular dermal matrix.* Plast Reconstr Surg, 2013. **132**(5): p. 1057-66.

[26] Davila, A.A., et al., *Human Acellular Dermis versus Submuscular Tissue Expander Breast Reconstruction: A Multivariate Analysis of Short-Term Complications.* Arch Plast Surg, 2013. **40**(1): p. 19-27.

[27] Heidemann, L.N., et al., *Complications following Nipple-Sparing Mastectomy and Immediate Acellular Dermal Matrix Implant-based Breast Reconstruction-A Systematic Review and Meta- analysis.* Plast Reconstr Surg Glob Open, 2018. **6**(1): p. e1625.

[28] Peled, A.W., et al., *The effects of acellular dermal matrix in expander-implant breast reconstruction after total skin-sparing mastectomy: results of a prospective practice improvement study.* Plast Reconstr Surg, 2012. **129**(6): p. 901e-908e.

[29] Lohmander, F., et al., *Implant Based Breast Reconstruction With Acellular Dermal Matrix: Safety Data From an Open-label, Multicenter, Randomized, Controlled Trial in the Setting of Breast Cancer Treatment*. Ann Surg 2019;**269**:836 – 841.

regain its natural shape and appearance. The human ADMs provide reinforcement for weakened dermal/skin tissue, supplements thin and overly dissected tissue, and repairs the breast boundaries that were eliminated during the procedure, all with the objective intent of supporting the healing process and returning the patient to normal activities of daily living. Without the ADMs, capsular contracture may occur which can result in limited mobility and use of the arm on the affected side.

Cornerstone of the 1-stage procedure, helping women "obtain wholeness" sooner. Human ADMs have been reported to address various issues with previously-used implant-based breast reconstruction techniques, including subcutaneous placement and submuscular placement (both full muscle coverage or FMC and partial muscle coverage or PMC) of the breast implant, and became a cornerstone of immediate breast reconstruction over the last two decades.[30,31,32]

Enhanced cosmesis and other benefits. The introduction of human ADMs within breast reconstruction surgery has provided surgeons with alternative means to reinforce, support, protect, or cover and protect soft tissue weaknesses, thereby alleviating some significant complications. Several authors, including Salzberg[33] and Spear,[34] have reported enhanced outcomes, citing increased fill volumes and improved aesthetic outcomes. In addition, Nguyen, et al performed a quantitative evaluation of aesthetic outcomes of breast reconstruction with (58 patients) and without (53 patients) the use of ADM.[35] They found that the ADM group demonstrated significantly greater aesthetic outcomes compared to the non-ADM group, in particular for breast mound volume, placement, and inframammary fold definition. Sbitany and Langstein reported that ADMs not only offer consistently superior aesthetic outcomes, but that this may be related to the increased intraoperative fill volumes and reduced number of expansions needed.[36] Consequently, the result is reduced time to completion and a reliable, aesthetically-superior breast reconstruction.

Reduction in capsular contracture. While likely not included as part of the manufacturer's objective intent, human ADMs for breast reconstruction may afford additional benefits. A study performed by Leong, Basu, and Hicks investigated whether human ADMs might inhibit the inflammatory and profibrotic signaling, which is characteristic of breast capsule development and also help to decrease the risk of capsular contracture. Their hypothesis was supported by clinical evidence indicating that the risk of capsular contracture is lower in patients who undergo reconstruction that includes human ADMs.[37] Additionally, Paydar, Wirth, and Mowlds reported that

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[30] Chun, Y.S., et al., *Implant-based breast reconstruction using acellular dermal matrix and the risk of postoperative complications.* Plast Reconstr Surg, 2010. **125**(2): p. 429-36.

[31] Bertozzi, N., et al., *One-Stage Immediate Breast Reconstruction: A Concise Review.* Biomed Res Int, 2017. **2017**: p. 6486859.

[32] Chao, A.H., *A Review of the Use of Acellular Dermal Matrices in Postmastectomy Immediate Breast Reconstruction.* Plast Surg Nurs, 2015. **35**(3): p. 131-4; quiz 135-6.

[33] Salzberg CA. Nonexpansive immediate breast reconstruction using human acellular tissue matrix graft (AlloDerm). Ann Plast Surg. 2006 Jul. 57(1):1-5.

[34] Spear SL, Parikh PM, Reisin E, Menon NG. Acellular dermis-assisted breast reconstruction. *Aesthetic Plast Surg*. 2008 May. 32(3):418-25.

[35] Nguyen, K.T., et al., *Esthetic Outcomes of ADM-Assisted Expander-Implant Breast Reconstruction.* Eplasty, 2012. **12**: p. e58.

[36] Sbitany, H. and H.N. Langstein, *Acellular dermal matrix in primary breast reconstruction.* Aesthet Surg J, 2011. **31**(7 Suppl): p. 30S-7S.

[37] LEONG, M.; BASU, C. B.; HICKS, M. J. Further evidence that human acellular dermal matrix decreases inflammatory markers of capsule formation in implant-based breast reconstruction. **Aesthetic Surgery Journal**, [s. l.], v. 35, n. 1, p. 40–47, 2015. Disponível em:

the protection ADMs afford against capsular contracture ultimately saves time and money and anecdotally results in improved patient comfort and satisfaction.[38] Other studies have noted the decreased occurrence of capsular contracture,[39,40,41,42] suggesting that ADMs may have an inhibitory effect on the inflammatory and profibrotic signaling associated with breast capsule development.[43]

Benefit for women receiving postmastectomy radiation therapy. Peled et al noted that human ADMs might provide particular benefit in patients who received postmastectomy radiation therapy.[44]

Overall risk-benefit evaluation.

In addition to the various studies detailing particular risks and benefits to the use of human ADMs for breast reconstruction, additional studies have examined the overall risk benefit profile, cost-savings, as well as insurance coverage. Each of those additional research topics provide greater support for the continued use of human ADMs within breast reconstruction.

Risk-benefit evaluation. Using updated data (i.e. reports published from 2011 to 2014), Lee, et al sought to reappraise the impact of ADM usage in implant-based breast reconstruction procedures, both in terms of benefits and risks.[45] Based on data from 23 studies comprising 6199 cases, they found that while the risk of infection, seroma, and mastectomy flap necrosis were slightly increased, there was no increased risk in total complications, implant loss, or unplanned reoperation. Moreover, they found a significantly decreased risk of capsular contracture, as well as implant malposition. They state that "…the increasing risks for serious complication and overall morbidity related to ADM use might not be remarkable, while its benefits for preventing late complications and improving expander dynamics might be appreciable." They therefore conclude that ADM usage in implant-based breast reconstruction is reliable and advantageous.

Cost-savings. In addition to the reported clinical benefits, ADM usage in breast reconstruction presents a more cost-effective option than reconstructive procedures without ADM, despite higher initial costs. This is because, when considering long-term outcomes, such as aesthetic benefits and the lack of the need for revision procedures,

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<http://search.ebscohost.com.contentproxy.phoenix.edu/login.aspx?direct=true&db=mdc&AN=25568233&site=eds-live>. Acesso em: 17 abr. 2019.

[38] Paydar KZ, Wirth GA, Mowlds DS. Prepectoral Breast Reconstruction with Fenestrated Acellular Dermal Matrix. Plastic and Reconstructive Surgery - Global Open. 2018;6(4):e1712. doi: 10.1097/GOX.0000000000001712.

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[40] Cheng, A., C. Lakhiani, and M. Saint-Cyr, *Treatment of capsular contracture using complete implant coverage by acellular dermal matrix: a novel technique.* Plast Reconstr Surg, 2013. **132**(3): p. 519-29.

[41] Spear, S.L., et al., *Nipple-sparing mastectomy for prophylactic and therapeutic indications.* Plast Reconstr Surg, 2011. **128**(5): p. 1005-14.

[42] Namnoum, J.D. and H.R. Moyer, *The role of acellular dermal matrix in the treatment of capsular contracture.* Clin Plast Surg, 2012. **39**(2): p. 127-136.

[43] Basu, C.B., M. Leong, and M.J. Hicks, *Acellular cadaveric dermis decreases the inflammatory response in capsule formation in reconstructive breast surgery.* Plast Reconstr Surg, 2010. **126**(6): p. 1842-7.

[44] Peled, A.W., et al., *The effects of acellular dermal matrix in expander-implant breast reconstruction after total skin-sparing mastectomy: results of a prospective practice improvement study.* Plast Reconstr Surg, 2012. **129**(6): p. 901e-908e.

[45] Lee, K.T. and G.H. Mun, *Updated Evidence of Acellular Dermal Matrix Use for Implant-Based Breast Reconstruction: A Meta-analysis.* Ann Surg Oncol, 2016. **23**(2): p. 600-10.

the overall expense is lower than with non-ADM reconstructive procedures.[46,47] Kankam et al[48] recently noted that, since the introduction of the use of human ADMs for breast reconstruction at their center, "more breast reconstructions have been of the implant-only type with consequent reductions in the more complex and expensive autologous techniques", with similar complication rates. According to a recent review article,[49] principal advantages include the potential enhancement of cosmesis in breast reconstruction, amelioration of late or irradiation-induced contracture, improved long-term correction of complications following aesthetic revisionary surgery and cost-savings imparted by the direct-to-implant breast reconstruction model.

Standard of care. Likely due to the overall risk-benefit profile and known cost-savings, human ADMs are the proven standard of care. Major U.S. payers (e.g. Anthem, CIGNA, Blue Cross Blue Shield, and Aetna) currently regard the use of acellular dermal matrix with breast reconstruction as a clinically supported and clearly reimbursable use, where the tissue assists the surgeons in reconstructing the breast at the time of mastectomy in a process that improves cosmetic outcome and limits the need for further surgical procedures.[50,51,52,53]

Conclusion

As detailed within this analysis, not only does skin grafting have a long history of human use, but the use of human ADMs in breast reconstruction over the past two decades has provided a wealth of information regarding its overall safety and effectiveness. Numerous studies have highlighted that, overall, the use of human ADMs does not increase the risks of breast reconstruction procedures, while affording key benefits (e.g., ability to perform one-stage procedures allowing women to regain "wholeness" in a more expedited manner, enhanced cosmesis, reduction in capsular contracture, and assistance with healing after radiation therapy). Likely due to the overall risk-benefit profile, human ADMs for breast reconstruction are not only the standard of care but also covered by most major insurers.

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[47] Zenn, M., et al., *Optimizing Outcomes of Postmastectomy Breast Reconstruction With Acellular Dermal Matrix: A Review of Recent Clinical Data.* Eplasty, 2017. **17**: p.e18.

[48] Kankam, Hayden A.M. et al. *Trends in post-mastectomy breast reconstruction types at a breast cancer tertiary referral centre before and after introduction of acellular dermal matrices*. Journal of Plastic, Reconstructive & Aesthetic Surgery (2018) **71**, 21e27.

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