FDA Executive Summary

Prepared for the October 26 & 27, 2022 Meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee

Classification of Tissue Expanders and Accessories

Product Code: LCJ

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1. Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), the Food and Drug Administration (FDA) is convening the General and Plastic Surgery Devices Advisory Panel (the Panel) for the purpose of obtaining recommendations regarding the classification of tissue expanders and accessories, a pre-amendments device type which remains unclassified. Specifically, the FDA will ask the Panel to provide recommendations regarding the regulatory classification of tissue expanders and accessories under product code "LCJ". The device names and associated product codes are developed by the Center for Devices and Radiological Health (CDRH) in order to identify the generic category of a device for FDA. While most of these product codes are associated with a device classification regulation, some product codes, including "LCJ" remain unclassified.

FDA is holding this panel meeting to obtain input on the risks to health and benefits of the tissue expanders and accessories under product code "LCJ". The Panel will discuss whether the tissue expanders and accessories under product code "LCJ" should be classified into Class III (subject to General Controls and Premarket Approval) or Class II (subject to General and Special Controls). If the Panel believes that classification into Class II is appropriate for tissue expanders and accessories, the Panel will also be asked to discuss appropriate controls that would be necessary to mitigate the risks to health.

1.1 Current Regulatory Pathways

Tissue expanders and accessories are a pre-amendments, unclassified device type. This means that this device type was marketed prior to the Medical Device Amendments of 1976, but was not classified by the original classification panels. Currently these devices are being regulated through the 510(k) pathway and are cleared for marketing if their intended use and technological characteristics are "substantially equivalent" to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the product code.

1.2 Device Description

Tissue expanders are intended for temporary subcutaneous or submuscular implantation to develop surgical flaps or additional tissue coverage in a variety of surgical applications, such as breast reconstruction following mastectomy, treatment of underdeveloped breasts, scar revision, and treatment of tissue deformities or injuries. Tissue expanders are intended for temporary implantation not to exceed 6 months. Tissue expanders can be used in various anatomical locations, including breast, head, neck, calf, and others.

Each tissue expander is composed of an inflatable silicone elastomer outer shell with an injection port. Tissue expanders are available in many different shapes (e.g., round, rectangular, cylindrical, U-shaped, crescent), sizes, volume ranges, dimensions, and surface texture (e.g., smooth, textured).

In general, round tissue expander devices have been cleared for breast reconstruction after mastectomy, correction of an underdeveloped breast, scar

revision, and tissue defect procedures. Rectangular tissue expanders have been cleared for preparation for closure of defects after resection of large tumors (e.g., nevi, basiloma, etc.), scar correction if primary direct closure is not possible, and preloading of local flaps (e.g., at forehead).

Once implanted under the area to be expanded, the tissue expander is gradually filled with normal physiological saline (injection grade, with a concentration of 0.15M and a pH of 7.2-7.4) through the injection port (magnetic or palpable) over time, causing the surrounding tissue to stretch and expand. Tissue expanders may have multiple suture tabs for an option to suture to surrounding tissue.

Tissue expanders also have accessories such as port detectors, fluid dispensing systems, needle infusion sets, external fill ports or syringe assists. [1]

2. Regulatory History

The first product cleared under the product code "LCJ" was the Radovan Subcutaneous Tissue Expander (K771224), which was cleared on October 11, 1977. This product was found substantially equivalent to the pre-amendments device, Inflatable Type Silicone Mammary Prostheses, manufactured by Heyer-Schulte Corporation.

To date, FDA has cleared 48 tissue expander and accessories 510(k)s under the LCJ product code; 42 of the clearances are for tissue expanders while 6 clearances pertain to accessories for tissue expanders.

Please refer to Table 1 for a listing of the manufacturers, device names, and associated 510(k) submission numbers for cleared tissue expanders and accessories under product code "LCJ".

Table 1: 510(k) clearances for tissue expanders and accessories under product code "LCJ"

510(k) Number	Trade Name	Sponsor
K771224	RADOVAN SUBCUTANEOUS TISSUE EXPANDER	HEYER SCHULTE CORP.
K790842	SUBCUTANEOUS TISSUE EXPANDER	HEYER SCHULTE CORP.
K801042	SILASTIC BRAND PERCUTANEOUS SKIN EXPANDE	DOW CORNING CORP. HEALTHCARE INDUSTRIES MATERIALS
K833502	RADOVAN SUBCUTANEOUS TISSUE EXPANDER	AMERICAN HEYER SCHULTE

[1] Note that intraoperative, non-implantable devices such as elevators or dissectors that are intended for intraoperative tissue expansion only, are excluded from the scope of this product code.

510(k) Number	Trade Name	Sponsor
K840464	TISSUE EXPANDER	SURGITEK
K842883	RADOVAN TISSUE EXPANDER	MENTOR CORP.
K843704	MCGHAN TISSUE EXPANDER	MCGHAN MEDICAL CORP.
K843678	CREAT BRAND SKIN EXPANDER	AESTHETECH CORP.
K844813	MENTOR EXPANDER MAMMARY PROSTHESIS	MENTOR CORP.
K845036	TISSUE EXPANDERS FOR RECONSTRUC-SURGERY 3600	PROGRESS MANKIND TECHNOLOGY
K853014	MCGHAN TISSUE EXPANDER FILL KIT	MCGHAN MEDICAL CORP.
K854794	MCGHAN INTEGRAL VALVE TISSUE EXPANDER	MCGHAN MEDICAL CORP.
K862049	MENTOR FLAT-SPAN	MENTOR CORP.
K862203	MCGHAN MAGNA-SITE(TM) TISSUE EXPANDER	MCGHAN MEDICAL CORP.
K864184	MCGHAN LONGTERM MAMMARY EXPANDER/GEL-SALINE DESIGN	MCGHAN MEDICAL CORP.
K864185	MCGHAN LONGTERM MAMMARY EXPANDER RTV DESIGN	MCGHAN MEDICAL CORP.
K865033	BREAST PROSTHESIS (NON & INFLATABLE) SKIN EXPANDER	COX-UPHUFF INTL.
K870154	POREX(TM) TISSUE EXPANDER	POREX MEDICAL
K870754	MCGHAN TISSUE EXPANDER FILL SYSTEM	MCGHAN MEDICAL CORP.
K865056	CUI TISSUE EXPANDER VERSAFIL(TM) TISSUE EXPANDER	COX-UPHUFF INTL.
K884250	RADOVAN TISSUE EXPANDER (OPTION INTEGRAL INJECT.)	MENTOR CORP.
K884746	SURGITEK FLAT T-SPAN	MEDICAL ENGINEERING CORP.
K894495	SURGITEK(R) EXTERNAL FILL PORT	SURGITEK

510(k) Number	Trade Name	Sponsor
K894475	MENTOR TISSUE EXPANDERS W/TDMAC COATING	MENTOR CORP.
K903448	SURGITEK TEX-SPAN TEXTURED TISSUE EXPANDER	MEDICAL ENGINEERING CORP.
K905484	ACCU-TEC SYSTEM FOR TISSUE EXPANDER INJECTION PORT	MENTOR CORP.
K963066	MENTOR INJECTION PORT DETECTOR (IPD)	MENTOR CORP.
K974209	SILICONE TISSUE/INFLATABLE TISSUE EXPANDER	SPECIALTY SURGICAL PRODUCTS INC.
K982067	MAGNETIC PORT SILICONE TISSUE EXPANDER	SPECIALTY SURGICAL PRODUCTS INC.
K981852	SILIMED TISSUE EXPANDER	SILIMED LLC.
K983792	SEARE BIOMEDICAL SILICONE TISSUE EXPANDER	SEARE BIOMEDICAL CORP.
K983385	HUTCHISON INFLATABLE SILICONE TISSUE EXPANDERS	HUTCHISON INTL. INC.
K011500	MENTOR CONTOUR PROFILE TISSUE EXPANDER	MENTOR CORP.
K070303	SILICONE TISSUE EXPANDER	SPECIALTY SURGICAL PRODUCTS
K102806	NATRELLE 133 TISSUE EXPANDER WITH SUTURE TABS	ALLERGAN MEDICAL
K112534	LIFECELL TISSUE EXPANDER	LIFECELL CORP.
K130813	MENTOR CPX 4 BREAST TISSUE EXPANDERS AND MENTOR CPX 4 WITH SUTURE TABS BREAST TISSUE EXPANDERS	MENTOR CORP.
K131692	BLOSSOM SALINE DELIVERY ASSIST DEVICE	MARZ MEDICAL INC
K140383	ALLOX2 TISSUE EXPANDERS	SPECIALTY SURGICAL PRODUCTS INC.

510(k) Number	Trade Name	Sponsor
K142998	CPX Control Breast Tissue Expander	MENTOR WORLDWIDE LLC
K150777	Artoura Breast Tissue Expander	MENTOR WORLDWIDE LLC
K143354	Natrelle 133 Plus Tissue Expander	ALLERGAN INC.
K152496	CPX 4 Breast Tissue Expander	MENTOR WORLDWIDE LLC
K161176	ARTOURA Breast Tissue Expanders with Smooth Surface	MENTOR WORLDWIDE LLC
K161483	Unger Quad Injector	STRADIS HEALTHCARE
K182054	Natrelle 133S Tissue Expander	Allergan
K182335	CPX 4 Breast Tissue Expander with Smooth Surface	Mentor Worldwide LLC
K180826	Natrelle 133 Plus MICROCELL Tissue Expander	Allergan

2.1 Summary of Previous Classification Panel Meeting

On August 26, 2005, the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee met to discuss the classification of tissue expanders, among other unclassified pre-amendments devices.[2] FDA presented information on tissue expanders, including certain risks of use and potential risk mitigation measures. The identified risks included skin trauma, device failure, infection, adverse tissue reaction, and pain. The mitigation measures recommended included labeling, preclinical testing, sterility, and biocompatibility. Following the discussion, the Panel voted unanimously to recommend that the Agency classify tissue expanders as Class II medical devices with special controls and requiring 510(k) premarket notification. The panel members also recommended specialized labeling to caution surgeons about the use of these devices in children and in locations where blood vessel or airway constrictions could occur, such as the head and neck.

Since 2005, there have been new developments in implant-based breast reconstruction, including new knowledge of potential risks to health. This includes the risk of developing breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), which was discussed in the FDA Update on the Safety

[2] For additional details, please refer to a brief summary of the August 26, 2005 panel meeting, *available at* https://wayback.archive-it.org/7993/20170405192855/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralandPlasticSurgeryDevicesPanel/ucm124755.htm

of Silicone Gel-Filled Breast Implants[3] and subsequently at the General and Plastic Surgery Public Advisory Committee Meeting in August 2011.[4] To gather additional information about ALCL in women with breast implants, FDA established a registry in collaboration with the American Society of Plastic Surgeons referred to as the PROFILE registry (Patient Registry and Outcomes For breast Implants and anaplastic large cell Lymphoma etiology and Epidemiology).

In 2016, the World Health Organization (WHO) designated BIA-ALCL as a T-cell lymphoma that can develop following breast implants and noted that the exact number of cases remained difficult to determine due to significant limitations in world-wide reporting and lack of global breast implant sales data.[5]

On March 25 & 26, 2019, FDA held a Public Advisory Committee meeting to discuss the risks and benefits of breast implants intended for breast augmentation and reconstruction.[6] Although the focus of the meeting was on breast implants, there is a shared concern between breast implants and tissue expanders intended for use in the breast given the similar anatomical location of implantation. Tissue expanders are typically used in the initial stage prior to placement of breast implants, are made of the same materials, and potentially carry similar risks as breast implants. During the Open Public Hearing portion of the 2019 Advisory Committee meeting, a majority of the patients highlighted the importance of the informed consent process and knowing the benefits and risks of breast implants. The meeting also covered a range of important topics on breast implant safety, including characterization of BIA-ALCL incidence and risk factors and methods for assessing systemic symptoms referred to by patients as breast implant illness (BII). The panel members also discussed and made recommendations on FDA questions related to BIA-ALCL and BII including risk factors for BIA-ALCL and the importance of additional research on BII, including having an appropriate control group to investigate how the numbers reported in breast implant patients compare to the incidence in the general population.

On July 24, 2019, the U.S. Food and Drug Administration requested that Allergan, the manufacturer of a specific type of textured implant, recall specific models of its textured breast implants and textured tissue expanders from the U.S.

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[3] FDA Update on the Safety of Silicone Gel-Filled Breast Implants June 2011, *available at* https://www.fda.gov/media/80685/download

[4] For additional details on the 2011 General and Plastic Surgery Advisory Panel Meeting, please refer to the meeting materials, *available at* https://wayback.archive-it.org/7993/20170404141139/https:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralandPlasticSurgeryDevicesPanel/ucm252477.htm

[5] For additional details on BIA-ALCL, please refer to FDA's Questions and Answers about Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), *available at* https://www.fda.gov/medical-devices/breast-implants/questions-and-answers-about-breast-implant-associated-anaplastic-large-cell-lymphoma-bia-alcl

[6] For additional details on the 2019 General and Plastic Surgery Advisory Panel Meeting, please refer to the meeting materials, *available at* https://www.fda.gov/advisory-committees/advisory-committee-calendar/may-30-31-2019-general-and-plastic-surgery-devices-panel-medical-devices-advisory-committee-meeting

market due to the risk of BIA-ALCL.[7] Since then, FDA has also released press releases or safety communications on breast implant safety.[8,9]

Therefore, considering the significant developments with respect to new risks related to the use of breast implants and tissue expanders intended for breast reconstruction, FDA is convening this classification panel to discuss the current landscape of product technology, indications for use, safety and effectiveness, and risks to health, on which to base classification of tissue expanders, which can be used in the breast as well as other anatomical locations.

3. Indications for Use

The Indications For Use (IFU) statement identifies the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.

Tissue expander devices under the product code "LCJ" have been cleared for prescription use only and are not intended for use beyond six months. They are used for temporary subcutaneous or submuscular implantation to develop surgical flaps and additional tissue coverage.

The tissue expander devices under the product code "LCJ" have been cleared for the following indications specific to use in the breast:

- Breast reconstruction after mastectomy or other trauma
- Correction or treatment of an underdeveloped breast
- Treatment of soft tissue deformities
- Combined chest wall and breast deformities

In addition to the listed indications which are specific to use in the breast, some tissue expander devices under the product code "LCJ" have been cleared for the following specific non-breast indications:

- Limb reconstruction
- Scar revision
- Tissue defect procedures: congenital deformities, cosmetic defects
- Correction of burn sequelae, baldness surgery, facial tumors, moles, and other skin blemishes

[7] See FDA news release, 'FDA takes action to protect patients from risk of certain textured breast implants; requests Allergan voluntarily recall certain breast implants and tissue expanders from market', *available at* https://www.fda.gov/news-events/press-announcements/fda-takes-action-protect-patients-risk-certain-textured-breast-implants-requests-allergan

[8] See FDA news release, 'FDA Strengthens Safety Requirements and Updates Study Results for Breast Implants', *available at* https://www.fda.gov/news-events/press-announcements/fda-strengthens-safety-requirements-and-updates-study-results-breast-implants

[9] See FDA Safety Communication, 'Breast Implants: Reports of Squamous Cell Carcinoma and Various Lymphomas in Capsule Around Implants', *available at* https://www.fda.gov/medical-devices/safety-communications/breast-implants-reports-squamous-cell-carcinoma-and-various-lymphomas-capsule-around-implants-fda?utm_medium=email&utm_source=govdelivery

- Expand tissue to aid in the primary closure of defects such as nevi and lesions, and to recruit additional tissue within a designed adjacent flap by expansion
- Tattoo and other anomaly removal
- Facial reconstruction, and treatment of decubitus ulcer

Some tissue expanders may include indications for breast and non-breast use.

The accessories to the tissue expanders have been cleared for the following indications:

- Detecting the location of the remote injection port or integral injection port
- Assisting the clinician in delivery of sterile saline into the surgically-placed, sub-dermal, temporary, removable tissue expander

4. Clinical Background

4.1 Disease Characteristics

Tissue expansion is a procedure used in surgeries when there is not enough skin or tissue coverage to achieve the intended outcome. Tissue expanders are intended for temporary subcutaneous or submuscular implantation near the area to be repaired and then are gradually filled with saline to develop surgical flaps or additional tissue coverage over time. Tissue expanders are commonly used for breast reconstruction following mastectomy or other trauma, repair of congenital or aesthetic tissue defects and other procedures. Tissue expanders may also be used in other anatomical regions, such as the head, neck, and calf.

4.2 Patient Outcomes

Patient outcomes following tissue expansion may be based on a combination of clinical parameters including the amount of skin or tissue stretched, the ability of the tissue to accommodate an implant, and tissue necrosis. The patient may be asked about pain, functional status, and quality of life.

4.3 Currently Available Treatment

To determine whether a tissue expander is used in surgery, the following are considered: clinical presentation and standard of care, the patient's underlying condition or disease, patient preference, the patient's medical history (smoking status, connective tissue disease, etc.), surgeon preference, and the amount of tissue coverage needed to achieve the desired clinical outcome. There are several alternatives to using tissue expanders in surgery. Alternatives can include: no reconstruction, external prosthesis, autologous tissue reconstruction, or not using a tissue expander. For tissue expanders specifically used in the breast, a direct breast implant is an additional alternative treatment.

4.4 Risks

FDA has identified the following risks to health associated with *all tissue expanders*:

Table 2: Risks to Health and Descriptions/Examples for *All Tissue Expanders*

Identified Risk	Description/Examples
Skin trauma	Device malposition or over inflation with saline may lead to skin trauma such as necrosis, thinning, sloughing, and extrusion.
Device malfunction or device failure leading to reoperation	Device malfunction, such as rupture/leakage, over inflation or failure to inflate, may require reoperation or explantation. Additional risks associated with reoperation include anesthesia risk, surgical time operation, patient dissatisfaction, infection, delay in treatment, scarring, and psychological burden.
Infection	Inadequate device sterilization or packaging integrity may lead to infection that may lead to additional surgical procedures.
Adverse tissue reaction	Device material(s) may elicit adverse tissue reactions, such as allergic reaction, toxicity, and foreign body response.
Pain or discomfort	This can result from device usage.

FDA has identified the following risks to health associated with *tissue expanders that are used in the breast*:

Table 3: Additional Risks to Health and Description/Examples for *Tissue Expanders that are used in the Breast*

Identified Risk	Description/Examples
Delay in adjunctive treatment or therapies	The potential to delay chemotherapy or other adjunctive cancer treatment/therapies to resolve any potential complications from the tissue expander use, such as infection.
Breast Implant Illness (BII)	Breast Implant Illness has been reported following the implantation/presence of tissue expander in the breast. See details below.
Breast Implant- Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)	Breast Implant- Associated Anaplastic Large Cell Lymphoma may develop from the implantation/presence of tissue expander in the breast. See details below.

Risk of Breast Implant Illness (BII) –
Some women have reported a variety of systemic symptoms following reconstruction or augmentation with breast implants, with or without prior implantation of tissue expanders. The term "breast implant illness" or "BII" has been used to describe these symptoms, which include but are not limited to, fatigue, problems with memory or concentration ("brain fog"), joint and muscle pain, hair loss, weight changes, anxiety, and depression. BII was discussed at the 2019 Panel Meeting.[10] The BII discussion focused on the constellation of symptoms reported by patients and the lack of defined diagnostic criteria for BII. The Panel indicated that many of the symptoms reported have other causes and stressed the importance of an appropriate control group to investigate how the numbers reported in breast implant patients compare to the incidence in the general population. The Panel also noted that there may be multiple factors which could affect these symptoms including genetic predisposition and patient and family history. Research continues to be performed to better understand any potential association with breast implants and tissue expanders. Currently, however, BII is not recognized as a formal medical diagnosis and there are no specific tests or recognized criteria to define or characterize it.

Risk of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) – In 2011, the FDA identified a possible association between breast implants and the development of anaplastic large cell lymphoma (ALCL). In 2016, the World Health Organization (WHO) designated breast implant-associated anaplastic large cell lymphoma as a T-cell lymphoma that can develop following breast implants.[11] BIA-ALCL has been diagnosed in patients between 4 months and 25 years from the time of implantation, with a median time to diagnosis of 9.3 years after implantation.[12] Among patients in the PROFILE registry, BIA-ALCL has been diagnosed between 0.08 years (29 days) and 27 years since implantation of the current device, with a median time to diagnosis of 9 years after implantation. Among patients with complete data in the PROFILE registry, time between device implantation and BIA-ALCL diagnosis range from 2 to 44 years, with a median time to diagnosis of 11 years.[13]

Many tissue expanders are intended for breast reconstruction after mastectomy or other trauma. These tissue expanders are commonly used in two-stage breast reconstructions where an initial temporary implantation of a tissue expander is

[10] For additional details on the 2019 General and Plastic Surgery Advisory Panel Meeting, please refer to the meeting materials, *available at* https://www.fda.gov/advisory-committees/advisory-committee-calendar/may-30-31-2019-general-and-plastic-surgery-devices-panel-medical-devices-advisory-committee-meeting
[11] Swerdlow, Steven H., et al. "The 2016 revision of the World Health Organization classification of lymphoid neoplasms." *Blood, The Journal of the American Society of Hematology* 127.20 (2016): 2375-2390.
[12] Brody GS, Deapen D, Taylor CR, Pinter-Brown L, House-Lightner SR, Andersen JS, Carlson G, Lechner MG, Epstein AL. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. Plast Reconstr Surg. 2015 Mar;135(3):695-705.
[13] McCarthy CM, Loyo-Berríos N, Qureshi AA, Mullen E, Gordillo G, Pusic AL, Ashar BS, Sommers K, Clemens MW. Plast Reconstr Surg. 2019 Mar;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):65S-73S.

later replaced with a breast implant following a period of gradual inflation. Currently, the risk of BIA-ALCL is largely associated with breast implants, and there is limited information to date on whether temporary exposure to tissue expanders may contribute to that risk.[14] Because the average time from implantation to BIA-ALCL diagnosis is 8 to 10 years and tissue expanders are not intended for implantation beyond 6 months, the inherent timeframe of BIA-ALCL pathogenesis may preclude case reports of tissue expanders present at the time of BIA-ALCL diagnosis. Thus, direct correlation between tissue expanders and BIA-ALCL diagnosis may be difficult to establish. Since the launch of the PROFILE registry in 2012, 186 distinct cases of BIA-ALCL were reported in the United States between August 2012 and March 2018. Among the 89 patients with complete data, all had a breast implant at the time of BIA-ALCL diagnosis. However, 38 of these 89 patients have a history of multiple prior device exposure, and 31 patients have a history of prior temporary tissue expanders. Of the five cases reported in the PROFILE registry between August 2021 and March 2018 in which the diagnosis of BIA-ALCL was made in a patient with a smooth shell breast implant, four patients had a history of prior implantation with a textured permanent implant and one patient had a history of prior textured tissue expander. In the literature, a case of BIA-ALCL was reported in a patient who had a textured breast tissue expander followed by a smooth breast implant.[15] Although the risk of BIA-ALCL is higher for textured surface implants versus smooth surface implants, the overall etiology of BIA-ALCL is not known.[16]

The etiology and pathogenesis of BIA-ALCL remain poorly understood. Potential impetuses for BIA-ALCL, as postulated in the literature based on limited scientific data, includes implant surface texture, patient's genetic predisposition, and the presence of bacterial endotoxins on implant surface. While there have been more Medical Device Reports (MDRs) submitted to FDA of BIA-ALCL associated with textured breast implants, there have also been reports associated with smooth breast implants. Given the wide variety of manufacturing methods (e.g., salt lost, imprinting, etc.) for modifying breast implant surfaces to create texturing and other surface features, combined with the lack of standardized method for characterizing implant surface, it is challenging to correlate the degree of implant surface texture with the risk of BIA-ALCL. As tissue expanders and breast implants often have nearly identical constructions as to shell materials, shape, size, and surface texture, tissue expanders may elicit similar immune and fibrotic responses when implanted. Given tissue expanders intended for use in the breast are intended to be temporary devices that are often replaced with permanent implants, it is unclear whether temporary exposure to tissue expanders may contribute to long term safety risks (e.g., BIA-ALCL, BII). Additional

[14] Medical Device Reports of Breast Implant-Associated Anaplastic Large Cell Lymphoma, *available at* https://www.fda.gov/medical-devices/breast-implants/medical-device-reports-breast-implant-associated-anaplastic-large-cell-lymphoma

[15] Akhavan AA, Wirtz EC, Ollila DW, Bhatt N. Plast Reconstr Surg. 2021 Aug 1;148(2):299-303.

[16] See FDA webpage, 'Questions and Answers about Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)', *available at* https://www.fda.gov/medical-devices/breast-implants/questions-and-answers-about-breast-implant-associated-anaplastic-large-cell-lymphoma-bia-alcl

research is needed on devices that are intended to be implanted into the breast to assess for any possible relation to BIA-ALCL.

FDA has identified the following risks to health associated with *accessories to tissue expanders*:

Table 4: Risks to Health and Description/Examples for *Accessories to Tissue Expanders*

Identified Risk	Description/Examples
Skin trauma	Needle injection may lead to minor bruising, bleeding, or other injury to tissue. Inaccurate reading from port detector may lead to bleeding if injection made at wrong location.
Device malfunction leading to increased operative time	Inaccurate reading from port detector may lead to rupture/leakage of tissue expander or damage/bleeding to surrounding blood vessels or tissues if injection made at wrong location. Needle misalignment may lead to rupture/leakage of tissue expander if needle is inserted at incorrect angle. These examples may lead to increased operative time and additional risks, such as increased anesthesia.
Infection	Inadequate device sterilization or packaging integrity may lead to infection that may lead to additional surgical procedures.
Adverse tissue reaction	Device material(s) may elicit adverse tissue reactions, such as allergic reaction, toxicity, and foreign body response.
Pain or discomfort	This can result from device accessory usage.

The Panel will be asked whether this list is a complete and accurate list of the risks to health presented by tissue expanders and accessories under product code "LCJ" and whether any other risks should be included in the overall risk assessment of the device type. The Panel will also be asked whether the risks identified above for tissue expanders intended for use in the breast would also apply to other tissue expanders used in the breast, regardless of technological characteristics.

5. Literature Review

5.1 Methods

A systematic literature review was conducted in an effort to gather any published information regarding the safety of tissue expanders that are under product code "LCJ."

Online literature searches were performed in two electronic databases: EMBASE and PubMed. The search used the following term: tissue expander. The search was limited to human clinical studies published in the English language, with publication dates between April 1, 2005 and April 1, 2022. Database filters were used to exclude laboratory studies, animal studies, economic/cost-effectiveness analyses, non-clinical trials (e.g., narrative reviews, conference abstracts, editorials), case series/single-arm studies (i.e., ≥10 patients) and case reports (i.e., ≤ 9 patients). Appendix A contains additional details on the search strategy.

5.2 Results

The search yielded 2,202 initial literature references. There were no duplicate articles found in the search. Following a review of the titles and abstracts, a total of 357 articles remained for full text review. Of these, 18 articles were determined to be relevant to the safety and effectiveness of tissue expanders. The number of each excluded criterium is also summarized in the flow diagram in Appendix B. The 18 selected studies consisted of 10 retrospective studies, 5 non-randomized prospective studies, 2 systematic literature reviews and 1 randomized controlled study. Of the 18 included studies, 17 studies examined the use of tissue expanders in the breast[i-xvii] and 1 study examined tissue expanders in dentistry.[17] Note that because tissue expanders have not been cleared for use in dental areas, the single study that examined tissue expanders in dentistry was excluded from the search results for the analysis below. Therefore, 17 literature articles (studies) were reviewed for the purposes of this literature search on tissue expanders.

None of the articles discussed accessories associated with tissue expanders. The included studies reported on 59,386 total patients whose mean ages ranged from 43.6 to 61.1 years.

Table 13 in Appendix C provides full details on the individual selected studies.

5.3 Adverse Events Associated with Tissue Expanders

Adverse Events Associated with Use in Breast

Majority of the included studies assessing tissue expanders for use in the breast reported complications.

[17] Byun SH, Kim SY, Lee H, et al. Soft tissue expander for vertically atrophied alveolar ridges: Prospective, multicenter, randomized controlled trial. Clin Oral Implants Res. Jul 2020;31(7):585-594. doi:10.1111/clr.13595

Table 5 below lists the outcomes that were reported by the 17 included studies assessing tissue expanders for use in the breast.

Table 5: Outcomes Reported in Articles for Tissue Expanders for the Breast

Complication/Adverse Event in Breast Reconstruction	Number of Studies where Complication was Reported	Adverse Event Rate or Rate Range Reported in Study
Infection	12/17	71%
Explantation	9/17	53%
Skin trauma	8/17	47%
Unspecified infection	5/17	0.7%-7.1%
Overall/any complications	4/17	5.4%-26.6%
Mastectomy flap necrosis	6/17	1.9%-8.5%
Reoperation	6/17	35%
Seroma	6/17	0.71-7.1%
Device failure	5/17	29.5%
Hematoma	4/17	0%-2.2%
Surgical site infection (SSI)	4/17	0.6%-56.0%
Nipple necrosis	2/17	5.8%-12%
Post-first stage operation	2/17	1.4%-42.4%
Reconstruction failure	2/17	2.7%-7.1%
Revision surgery	2/17	4%-59.2%
Severe capsular contracture	2/17	3.8%-13.8%
Unspecified explantation	2/17	2.3-3.6%
Wound dehiscence	2/17	1.7%-2.2%
Wound infection/complication	2/17	10.4% and 3.9%
Autologous reconstruction	1/17	6.8%
Bleeding complications	1/17	0.64%
Breast implant explantation	1/17	3.8%
Cellulitis	1/17	3.4%
Complication requiring hospitalization	1/17	6.5%
Complication requiring re-evaluation	1/17	3.1%
Delayed wound healing	1/17	0.8%
Displacement	1/17	8.4%-9.8%
Expander extrusion	1/17	0.78%
Explantation after cellulitis	1/17	60%
Implant dystopia	1/17	0.8%
Implant failure	1/17	2.4%
Implant infection	1/17	7.4%
Implant or expander removal	1/17	24.6%
Implant rupture	1/17	2.9%
Post second stage operation	1/17	22.6%
Prolonged drain usage post first stage operation	1/17	8.4%-34.8%
Re-operative complications	1/17	15.5%

Reoperation within 30 days	1/17	6.9%
Rippling	1/17	11.8%
Surgical complications	1/17	6.7%
Major complication	1/17	1.6%
Minor cellulitis	1/17	7.1%
Prosthesis failure	1/17	0.8%
Unspecified reconstruction	1/17	14.1%
Wound disruption	1/17	0.4%
1 or more additional procedures	1/17	76.2%
3 or more additional procedures	1/17	35.8%

There were no BIA-ALCL cases found in the included studies for this systemic literature review; however, the literature search excluded certain studies, including those with less than 100 patients per study arm. A search of the excluded articles was conducted to see if there were any articles that may have discussed BIA-ALCL. Among the excluded articles, one study evaluated BIA-ALCL patients at a single institution in a prospective manner to report patient presentation, clinical course, treatment, and outcomes.[18] The Tevis et. al. article identified 52 women with pathologically confirmed BIA-ALCL. When available, details of tissue expander placement were recorded in the study, however the details of the placement were not included in the article.

Adverse Events Associated with Use in Non-Breast Location

None of articles analyzed for our literature review on tissue expanders evaluated a use outside of the breast.

5.4 Effectiveness Associated with Tissue Expanders

Tissue expander are intended to be used for breast reconstruction after mastectomy or other trauma, correction or treatment of an underdeveloped breast, treatment of soft tissue deformities, combined chest wall and breast deformities, limb reconstruction, scar revision, tissue defect procedures: congenital deformities, cosmetic defects, correction of burn sequelae, baldness surgery, facial tumors, moles, and other skin blemishes, to expand tissue to aid in the primary closure of defects such as nevi and lesions, and to recruit additional tissue within a designed adjacent flap by expansion, tattoo and other anomaly removal, facial reconstruction, and treatment of decubitus ulcer. In the 17 articles used above, tissue expanders were used for expansion, however, the articles did not describe the overall effectiveness of the tissue expander.

[18] Tevis SE, Hunt KK, Miranda RN, et al. Breast Implant-associated Anaplastic Large Cell Lymphoma: A Prospective Series of 52 Patients. Article. Ann Surg. 2022;275(1):E245-E249. doi:10.1097/SLA.0000000000004035

5.5 Overall Literature Review Conclusions

The published, peer-reviewed clinical evidence considering use of tissue expanders focused on its use in the breast. No articles provided information on tissue expander use in non-breast locations cleared by the FDA, such as head or calf. Ten of the 17 included studies used a retrospective study design. Observational study designs (e.g., case-control studies, cohort studies), even those that age- and sex-match patient groups, are prone to several biases (e.g., confounding and selection) because patient and provider characteristics are not balanced across study arms. Study funding source, another potential source of bias, was not reported in 11 studies, was reported as not funded in 2 studies, and the remaining 4 studies were funded by non-biased sources. The strength of the evidence base for tissue expanders is unclear at best.

With respect to complications and adverse events, skin trauma, device failure, infection, explantation, and reoperation were each reported by a minimum of 6 studies. None of the studies originally yielded from this search reported BIA-ALCL or any cancer or lymphoma outcomes. One article (Tevis et al.), upon review after initial exclusion, confirmed BIA-ALCL in 52 women but reported limited clinical information. Other adverse events, such as over expansion, bleeding complications, and displacement, were inconsistently, and often vaguely, reported and ranged from mild (e.g., minor complications, unspecified) to severe (e.g., hospitalization).

For subgroup analyses, only one study (Chiu et. al.) assessed textured versus smooth tissue expanders. For most reported outcomes, the authors were unable to find a statistically significant between-group difference between the two textures. However, these results are from one study (Chie et. al.), so the evidence base for that comparison is very limited. For the comparison between patients with and without breast cancer, only one study (ElSherif et. al) enrolled both breast cancer patients and non-breast cancer patients and reported findings based on those subgroups. In this ElSherif et. al. study, breast cancer patients were compared to patients who were undergoing breast reconstruction for prophylactic purposes. This included 259 patients who received a tissue expander and 312 patients who received a direct breast implant. The authors were unable to find a statistically significant between-group difference in outcomes (e.g., early and late surgical site infection (SSI)) for the two groups of patients. Again, for this subgroup analysis, the evidence base for breast cancer patients versus non-breast cancer patients is extremely limited.

When assessing the comparative rates and types of complications/adverse events associated with tissue expander use in breast surgery versus non-breast surgery, all of the 17 studies evaluated tissue expander use in the breast and a comparison to study(ies) that evaluated tissue expander in non-breast region could not be made.

Regarding the rates and types of complications/adverse events associated with tissue expanders affected by duration of use, no studies formally compared rates/types of adverse events in patient groups with different durations of tissue expander placement. However, one study (Bae et. al.) did report a multivariate analysis which demonstrated "the interval between the first- and second-stage operation (time of tissue expander implantation) was inversely associated with the risk of breast implant rupture. Cases with an interval ≤6 months were associated with higher risks for breast implant rupture than those with ≥7 months, after adjusting for other variables." Because no between group statistically significant difference was found for breast implant rupture based on tissue expander brand, this variable was not included in the multivariate analysis.

An additional literature search was conducted to determine if there were any publications describing cases of ALCL with medical devices other than breast implants. FDA presented results from a prior literature search on this topic, conducted through February 28, 2019, at the March 25-26, 2019 General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting. The results showed that ALCL has been associated with devices other than breast implants in the literature, including metal implants, PTFE (Polytetrafluoroethylene) polymer vascular graft, gluteal implants, and lap band.[19] For this updated search, the Embase and PubMed/MEDLINE databases were searched for studies published from January 1, 2019 through June 28, 2022. Two case report studies described ALCL attributed to non-breast implants, including a metal femoral rod and fixation screws and a gluteal implant.[20,21] Time from implant to ALCL diagnosis was 10 years for the femoral implant and approximately 20 years for the gluteal implant. Both patients did not have a history of cancer. The quality and quantity of the overall evidence presented in the studies is low due to only two non-US case reports; however, the reports provide additional evidence of non-breast implant-related ALCL since the last literature search in 2019, which suggests the issue may warrant ongoing surveillance.

Overall, the systematic literature search for tissue expanders returned 17 articles, with all 17 articles reporting on tissue expanders used in the breast. Most articles report complications when tissue expanders are use in the breast. A major limitation of this search was that the search excluded case report studies, which included 1 study that discussed BIA-ALCL. However, the systematic literature search supports the conclusion that there are additional risks associated with use of tissue expanders in the breast.

[19] See FDA presentation, "Benefits and Risks of Breast Implants," March 25-26, 2019, available at https://www.fda.gov/media/122961/download

[20] Mendes J, Jr., Mendes Maykeh VA, Frascino LF, Zacchi FFS. Gluteal Implant-Associated Anaplastic Large Cell Lymphoma. *Plast Reconstr Surg.* 2019;144(3):610-613.

[21] Parkhi M, Singh C, Kumar R, Malhotra P, Bal A. Systemic ALK-positive anaplastic large cell lymphoma involving implant site: a fortuitous association. *Autops Case Rep.* 2021;11:e2021296

6. Risks to Health Identified through Medical Device Reports (MDRs)

6.1 Overview of the MDR System

The MDR system provides FDA with information on medical device performance from patients, health care professionals, consumers and mandatory reporters (manufacturers, importers and device user facilities). The FDA receives MDRs of suspected device-associated deaths, serious injuries, and certain malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDRs can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, duplicated or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about the frequency of device use. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of these limitations, MDRs comprise only one of the FDA's tools for assessing device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

6.2 MDR Data: Tissue Expanders

Individual MDRs for tissue expanders are reported through FDA's Manufacturer and User Facility Device Experience (MAUDE) Database, which houses mandatory reports from medical device manufacturers, importers and user facilities, as well as voluntary reports from entities such as health care professionals, patients and consumers.

A search of MDRs was performed, without a date range, to include all MDRs received under the product code "LCJ" up to April 1, 2022. The search resulted in the identification of 3,068 unique MDRs for inclusion in this analysis. 1,587 of the 3,068 MDRs provided data on patient age, and the median patient age in those reports was 49.2 years. Of the 3,068 MDRs, there were 207 voluntary MDRs, 2,838 reports submitted by manufacturers, and 23 MDRs submitted by user facilities. Note, the individual submitting the MDR chooses the category for the event type (serious injury or malfunction) of MDR submitted. Of the 3,068 MDRs, there were 2,544 serious injury MDRs, 509 malfunctions, 5 death MDRs, and an additional 10 MDRs that had a blank or other listed as the event type.

Additionally, there were 5,573 serious injury MDRs for the product code LCJ that were received through the Alternate Summary Reporting (ASR) Program[22] from June 9, 2000 to December 5, 2018. The adverse events reported through the ASR program were similar to the adverse events reported through the MAUDE database, summarized in more detail below. Please refer to Appendix D for a table listing the Top Patient Problem Codes submitted through ASR.

The analysis of MDRs associated with tissue expanders provided herein includes all events received by FDA through the standard individual MDR reporting mechanism.

Of the 3,068 MDRs included in the analysis, 3,052 report use in the breast and 16 report use in anatomical locations other than the breast. There were no MDRs on accessories associated with tissue expanders.

MDRs related to Tissue Expanders Used in the Breast

Of the 3,052 MDRs related to use in the breast, there were 2,531 serious injury reports, 506 malfunctions, and 5 deaths.

Of the 3,052 for the breast reports, there were 2,531 serious injury reports. The narratives for the serious injury MDRs can provide additional information on the events that occurred. The narratives of the serious injury reports were reviewed, and the serious injuries reported are summarized in Table 6 below. Note that each MDR narrative may describe multiple events, and therefore the number of events may not equal the number of MDRs. There were 176 MDRs that provide references to literature, but it is not clear whether the adverse events reported in the literature references refers to adverse events that have already been submitted to FDA.

Table 6: Summary of Serious Injury Reports for Tissue Expanders Used in the Breast

Serious Injury	MDRs
Deflation/Rupture/Leak	1,475
Infection	298
Defective	170
Seroma	68
No event narrative	56
Capsular Contracture	55
Pain	40
Systemic Symptoms, Breast Implant Illness (BII)	30

[22] The Alternate Summary Reporting (ASR) program enabled manufacturers of certain device types to submit quarterly summary reports of specific well known and well characterized events in lieu of individual reports of each such event. The ASR Program was in effect from 1997 through June 2019.

Serious Injury	MDRs
Inflammation (cellulitis, dermatitis, and mastitis)	32
Necrosis	23
Extrusion	16
User Error	13
Foreign body contamination	12
BIA-ALCL	8
Hematoma	8
Allergic response	7
Autoimmune disease	6
Abscess	5
Exposure	5
Lymphedema	3

The serious injuries reported from the MDR and listed in Table 6 above, are events that may be typically seen with tissue expanders use. Notably, there were reports of serious injuries for BII and BIA-ALCL. Of the 2,531 serious injury MDRs, 30 report of systemic symptoms BII. These reports included a description of symptoms including fatigue, brain fog, chronic pain, rashes, itching, and others. Many of the reports reported that symptoms improved or resolved when the tissue expanders were explanted. There were 8 MDRs that reported a BIA-ALCL diagnosis after the use of a tissue expander for the breast. Of these 8 reports, 5 MDRs describe use of a textured tissue expander followed by a permanent breast implant, 1 MDR describes the use of a textured tissue expander with no additional information on the history of other devices implanted, 1 MDR describes the use of a breast implant with no additional information on the history of other devices implanted, and 1 MDR describes the use of textured expanders followed by smooth implants. Refer to Appendix D that contains two tables providing additional details on the MDRs received reporting a diagnosis BII and BIA-ALCL after tissue expander use. As mentioned earlier, given tissue expanders intended for use in the breast are intended to be temporary devices that are often replaced with permanent implants, it is unclear whether temporary exposure to tissue expanders may contribute to long term safety risks (e.g., BIA-ALCL, BII).

Of the 3,052 for the breast reports, there were 506 malfunction reports. The narratives for the malfunction MDRs can provide additional information on the events that occurred. The narratives of the malfunction reports were reviewed, and the malfunction reported are summarized in Table 7 below. Note that each MDR narrative may describe multiple events, and therefore the number of events may not equal the number of MDRs. As the individual submitting the MDR chooses the event type, there may be similar adverse events identified under the serious injury table above (Table 6) and the malfunctions table below (Table 7)

(e.g. “rupture” is reported in both the serious injury category and the malfunction category).

Table 7: Summary of Malfunction MDRs for Tissue Expanders Used in the Breast

Malfunction	MDR Count
Deflated, rupture, leak	262
Defective	131
Foreign body	33
Use error	11
Literature	5
Infection	4
Capsular Contracture	4

Of the 3,052 MDRs for the breast, there were 5 deaths. Of the five MDRs that reported a death, two MDRs are for the same patient but reporting different devices, resulting in a total of four reported deaths. Of the four reported deaths, only one report provided an event narrative, which stated "partial necrosis of flap, wound infection, distant metastasis, tissue expander [TE] removal and death.” Another report provided the patient’s medical history, which includes cardiovascular disease, hypothyroidism, obesity, post-operative atelectasis, and productive cough. The remaining two MDRs that reported death provided no additional information.

MDRs related to Tissue Expanders Used in Anatomical Locations Other Than the Breast

Of the 3,068 MDRs included in the analysis, 16 MDRs reported adverse events with a tissue expander used in anatomical locations other than the breast. Of these 16 MDRs, there were 13 reports of serious injury and 3 reports of malfunctions. The anatomical sites for these 16 MDRs include:

- 3 for the skin
- 3 for the scalp
- 2 for the back
- 2 for the abdomen
- 2 for the thigh
- 1 for the head/neck
- 1 for the leg
- 1 for cleft face
- 1 for the calf

Of these 16 MDRs, deflation was reported in 12 of the MDRs, infection was reported in three, and one MDR did not report the type of adverse event. None of these 16 MDRs for tissue expanders used in anatomical locations other than the breast reported systemic symptoms or any type of lymphoma.

6.3 Overall MDR Review Conclusions

Overall, the MDR analysis shows that there are complications associated with the use of tissue expanders for all indications. The analysis shows that there are specific complications associated with the use of tissue expanders in the breast that may not be found when tissue expanders are used in other anatomical regions. In particular, the MDR analysis shows that there are several reports of BIA-ALCL and BII when tissue expanders are used in the breast.

7. Recall History

7.1 Overview of Recall Database

The Medical Device Recall database contains Medical Device Recalls classified since November 2002. Since January 2017, it may also include correction or removal actions initiated by a firm prior to review by the FDA. The status is updated if the FDA identifies a violation and classifies the action as a recall and again when the recall is terminated. FDA recall classification may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall. Therefore, the recall information posting date ("create date") identified on the database indicates the date FDA classified the recall, it does not necessarily mean that the recall is new.

7.2 Recall Results: Tissue Expanders

A total of ten recalls have been reported to date for devices with the product code "LCJ". This includes four class 1 recalls and six class II recalls[23]. To protect individuals from the increased risk of BIA-ALCL associated with Allergan BIOCELL textured breast implants, the FDA requested that Allergan recall its BIOCELL textured breast implants and textured tissue expanders on July 24, 2019. Allergan agreed and removed these products from the global market. This recall suggests that there may be additional risks associated with the use of tissue expanders in the breast. Aside from the Allergan BIOCELL recall, the other identified recalls are related to manufacturing errors and do not suggest additional risks associated with the use of tissue expanders.

The recalls are summarized below:

- Z-2457-2019, Z-2456-2019, Z-2455-2019, Z-2458-2019: These class I recalls were initiated due to FDA's updated global safety information concerning the

[23] Recalls are classified into a numerical designation (I, II, or III) by the FDA to indicate the relative degree of health hazard presented by the product being recalled. A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. A Class II recall is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. A Class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

higher incidence of anaplastic large cell lymphoma (BIA-ALCL) in patients who have textured breast implants.

- Z-2780-2016, Z-2781-2016: These class II recalls were initiated due to certain tissue expanders that may be packaged in boxes labeled for another model.

- Z-2747-2016, Z-2748-2016: These class II recalls were initiated due to certain tissue expanders that may be packaged in boxes labeled for the wrong size.

- Z-2103-2015, Z-2104-2015: These class II recalls were initiated due to tissue expanders that were shipped beyond the product shelf life.

8. Summary

In light of the information available, the Panel will be asked to comment on whether tissue expanders and accessories under product code "LCJ" meet the statutory definition of a Class III device in accordance with section 513 of the Food, Drug, and Cosmetic Act (FD&C Act), that is:

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or

- if the device presents a potential unreasonable risk of illness or injury

or to Class II, in which:

- general and special controls, which may include performance standards, postmarket surveillance, patient registries and/or development of guidelines, are sufficient to provide reasonable assurance of safety and effectiveness.

FDA proposes that tissue expanders intended for use in the breast meet the statutory definition of a Class III device because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of their safety and effectiveness. Additionally, tissue expanders intended for use in the breast present a potential unreasonable risk of illness or injury based on limited clinical information that has been obtained.

If the Panel does not agree that tissue expanders intended for use in the breast meet the statutory definition of a Class III device, the Panel will be asked for input regarding whether the available scientific evidence supports a Class II determination with special controls, including which special controls could be established to mitigate the known risks to health associated with these devices. If the Panel supports classification into

Class II, the Panel will further be asked to provide reasons for not recommending classification of the device into Class III.

FDA proposes that tissue expanders intended for use in other parts of the body (non-breast use) and accessories to tissue expanders meet the statutory definition of Class II device because general and special controls, which may include performance standards, postmarket surveillance, patient registries and/or development of guidelines, are sufficient to provide reasonable assurance of safety and effectiveness.

For the purposes of classification, FDA also considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;

2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

4. The reliability of the device.

Part (g)(1) of this regulation further states that it "is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into Class III."

The Panel will be asked whether they believe tissue expanders intended for use in the breast would be appropriately regulated as Class III. The Panel will also be asked whether they believe tissue expanders intended for use in other parts of the body (non-breast use) and tissue expander accessories would be appropriately regulated as Class II. If the Panel does not agree with FDA's proposed classification, the Panel will be asked to provide their rationale for recommending a different classification.

8.1 Reasonable Assurance of Safety for Tissue Expanders Intended for Use in the Breast

According to 21 CFR 860.7(d)(1), "there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against

unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

FDA has identified potential risks to health associated with tissue expanders intended for use in the breast, based on the currently reported adverse events. These include the following:

Table 8: Risks to Health and Description/Examples for Tissue Expanders Intended for Use in the Breast

Identified Risk	Description/Examples
Skin trauma	Device malposition or over inflation with saline may lead to skin trauma such as necrosis, thinning, sloughing, and extrusion.
Device malfunction or device failure leading to reoperation	Device malfunction may result in rupture or failure to inflate, which may require reoperation. Additional risks include those associated with reoperation such as anesthesia risk, surgical time operation, patient dissatisfaction, infection, delay in treatment, scarring, and psychological burden
Infection	Inadequate device sterilization or packaging integrity may lead to infection that may lead to additional surgical procedures.
Adverse tissue reactions	Device material(s) may elicit adverse tissue reactions, such as allergic reaction, toxicity, and foreign body response.
Pain or discomfort	This can result from device usage.
Delay in adjunctive treatment or therapies	The potential to delay chemotherapy or any adjunctive cancer treatment/therapies to resolve any potential complications from the tissue expander use, such as infection.
Breast Implant Illness (BII)	Breast Implant Illness has been reported following the implantation/presence of tissue expander in the breast.
Breast Implant- Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)	Breast Implant Associated Anaplastic Large Cell Lymphoma may develop from the implantation/presence of tissue expander in the breast.

The identified risks could result from the reported device-related adverse events including device leakage/rupture, over inflation, and inadequate sterilization.

This list may not be exhaustive. Given tissue expanders intended for use in the breast are intended to be temporary devices that are often replaced with permanent implants, it is unclear whether temporary exposure to tissue expanders may contribute to long term safety risks (e.g., BIA-ALCL, BII). The risks of BIA-ALCL and BII potentially occurring with tissue expanders intended for use in the breast may not be mitigated by special controls. The ability to have more stringent postmarket oversight typically associated with class III devices (such as annual reports and reports of manufacturing changes) can offer a means to monitor the devices and offer a reasonable assurance of safety.

The FDA will ask the Panel to comment on the risks to health identified and whether there are additional risks that should be considered for tissue expanders intended for use in the breast or if any of the identified risks should be removed. Additionally, the FDA will ask the Panel whether the evidence demonstrates a reasonable assurance of safety for tissue expanders intended for use in the breast.

8.2 Reasonable Assurance of Effectiveness for Tissue Expanders Intended for Use in the Breast

According to 21 CFR 860.7(e)(1), "there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific device, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

Breast reconstruction includes primary reconstruction to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality. Breast reconstruction also includes revision surgery to correct or improve the result of a primary breast reconstruction surgery. As evidenced in the literature, tissue expander surgery offers many benefits to both the patient and the surgeon. Use of a tissue expander provides options to the patients and surgeons, including placement of a breast implant, autologous tissue reconstruction, or tissue expander removal with no further reconstruction. Some patients choose to forgo tissue reconstruction for fear that it will make detection of recurrent breast cancer difficult. These patients favor tissue expander use with the understanding that the prosthesis can be removed if needed. This eases their concerns of oncologic safety and encourages them to consider the aesthetic benefits. Benefits for the surgeon include the ability to continue medical treatment for breast cancer immediately after surgery. Delayed reconstruction has the advantage of flexibility with chemotherapy and radiation and expediting treatment, which might make it the preferred reconstruction in patients with more advanced breast cancer. Patients are able to undergo radiation therapy after

delayed reconstruction with less risk of harm to the flap. Furthermore, delayed reconstruction helps ensure negative margins are obtained.[24]

The FDA will ask the Panel whether there is a reasonable assurance of effectiveness for tissue expanders intended for use in the breast.

8.3 Special Controls for Tissue Expanders Intended for Use in Other Parts of the Body (Non-Breast Use)

FDA believes that special controls, in addition to general controls, can be established to mitigate the risks to health identified, and provide a reasonable assurance of the safety and effectiveness for tissue expanders intended for use in other parts of the body (non-breast). Following is a risk/mitigation table, which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks:

Table 9: Summary of Risks to Health and Proposed Mitigations for Tissue Expanders Intended for Use in Other Parts of the Body (Non-Breast)

Identified Risk	Recommended Mitigation Measure
Skin trauma	Performance testing Labeling
Device malfunction or device failure leading to reoperation	Performance testing Labeling
Infection	Sterilization testing/validation/information Shelf-life validation Labeling
Adverse tissue reaction	Biocompatibility evaluation Labeling
Pain or discomfort	Labeling

Based on the identified risks and recommended mitigation measures, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness for tissue expanders intended for use in other parts of the body (non-breast use) under product code "LCJ":

1. The patient-contacting components of the device must be demonstrated to be biocompatible.
2. Performance data must demonstrate the sterility of patient-contacting components of the device.
3. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    i) Mechanical assessment of the shell (tensile strength, percent elongation, tensile set, and joint testing).

[24] Ilonzo N, Tsang A, Tsantes S, Estabrook A, Thu Ma AM. Breast reconstruction after mastectomy: A ten-year analysis of trends and immediate postoperative outcomes. Article. Breast. 2017;32:7-12. doi:10.1016/j.breast.2016.11.023

ii) Shell surface characterization (manufacturing methods, surface roughness/texturing)
iii) Injection site testing to show that tissue expander can be accurately accessed.
iv) Valve competency testing (if applicable) to demonstrate that valve integrity is maintained at in vivo loads.
v) Self-sealing patch testing (if applicable) to demonstrate a punctured patch can self-seal and maintain that self-seal for the duration of use.

4. Performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life.
5. Labeling must include:
    i) Information on how the device operates and the typical course of treatment.
    ii) Warning related to use beyond tissue tolerance which may result in tissue damage.
    iii) The risks and benefits associated with the use of the device
    iv) Post-operative care instructions.
    v) Alternative treatments.
    vi) Shelf life.

8.4 Special Controls for Tissue Expander Accessories

FDA believes that special controls, in addition to general controls, can be established to mitigate the risks to health identified, and provide a reasonable assurance of the safety and effectiveness for tissue expander accessories. Following is a risk/mitigation table, which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks:

Table 10: Summary of Risks to Health and Proposed Mitigations for Tissue Expander Accessories

Identified Risk	Recommended Mitigation Measure
Skin trauma	Performance testing Labeling
Device malfunction leading to increased operative time	Performance testing Labeling
Infection	Sterilization testing/validation information Shelf-life validation Labeling
Adverse tissue reaction	Biocompatibility evaluation Labeling
Pain or discomfort	Labeling

Based on the identified risks and recommended mitigation measures, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness for tissue expander accessories under product code "LCJ":

1. The patient-contacting components of the device must be demonstrated to be biocompatible.
2. Performance data must demonstrate the sterility of patient-contacting components of the device.
3. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use.
4. Performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life.
5. Labeling must include:
    i) Information on how the device accessory operates.
    ii) The risks and benefits associated with the use of the device accessory.
    iii) Shelf life.

8.5 Overview of Proposed Classification

As noted above, a device will be considered Class III if:

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

For tissue expanders intended for use in the breast, several risks to health have been identified based on the literature and adverse event reports received by FDA, but not all such risks may be known. Given the limited available information on the long-term effects of these devices when used in the breast, FDA does not believe that special controls can be established to mitigate the known risks to health associated with these devices. Therefore, FDA believes that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of tissue expanders intended for use in the breast. Additionally, FDA believes that these tissue expanders present a potential unreasonable risk of illness or injury, including BIA-ALCL, based on the limited clinical information that is available.

In addition, based on the safety and effectiveness information gathered by the FDA, the identified risks to health and recommended mitigation measures, we recommend that tissue expanders intended for use in other parts of the body (non-breast) and accessories to tissue expanders be regulated as Class II devices.

878.3505 Tissue Expanders

(a) *Identification.* A tissue expander is an inflatable silicone elastomer shell filled with normal physiological saline intended for temporary implantation to develop

surgical flaps or additional tissue coverage in surgical applications. Tissue expanders may have a smooth or textured surface and are filled through an injection port. A tissue expander is intended for temporary subcutaneous or submuscular implantation not to exceed 6 months. The device includes tissue expanders intended for use in the breast, tissue expanders intended for use in other parts of the body (non-breast), and accessories for tissue expanders.

(1) Tissue expanders intended for use in the breast are generally round in shape and have varying fill volume range, width range, height range, and projection range. They may have multiple suture tabs for an option to suture to surrounding tissue. They are intended for breast reconstruction after mastectomy or other trauma, correction or treatment of an underdeveloped breast, treatment of soft tissue deformities or a combined chest wall and breast deformities.

(2) Tissue expanders intended for other use in other parts of the body (non-breast) can have different shapes including rectangular, cylindrical, U-shaped, and crescent. They have varying fill volumes and dimensions. Tissue expanders for other parts of the body (non-breast) are intended for soft tissue expansion, such as scar revision, and treatment of tissue deformities or injuries, in anatomical locations other than the breast.

(3) Accessories common to tissue expanders in the breast and other anatomical areas can include port detectors, fluid dispensing systems, needle infusion sets, external fill ports, and syringe assists.

(b) *Classification.*
(1) Class III (premarket approval) when intended for use in the breast.

(2) Class II (special controls) when intended for use in other parts of the body (non-breast). The special controls for this device are:
1. The patient-contacting components of the device must be demonstrated to be biocompatible.
2. Performance data must demonstrate the sterility of patient-contacting components of the device.
3. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    i) Mechanical assessment of the shell (tensile strength, percent elongation, tensile set, and joint testing).
    ii) Shell surface characterization (manufacturing methods, surface roughness/texturing)
    iii) Injection site testing to show that tissue expander can be accurately accessed.
    iv) Valve competency testing (if applicable) to demonstrate that valve integrity is maintained at in vivo loads.

v) Self-sealing patch testing (if applicable) to demonstrate a punctured patch can self-seal and maintain that self-seal for the duration of use.

4. Performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life.
5. Labeling must include:
   i) Information on how the device operates and the typical course of treatment.
   ii) Warning related to use beyond tissue tolerance which may result in tissue damage.
   iii) The risks and benefits associated with the use of the device.
   iv) Post-operative care instructions.
   v) Alternative treatments.
   vi) Shelf life.

(3) Class II (special controls) for tissue expanders accessories. The special controls are:

1. The patient-contacting components of the device must be demonstrated to be biocompatible.
2. Performance data must demonstrate the sterility of patient-contacting components of the device.
3. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use.
4. Performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life.
5. Labeling must include:
   i) Information on how the device accessory operates.
   ii) The risks and benefits associated with the use of the device accessory.
   iii) Shelf life.

Based on the available scientific evidence, the FDA will ask the Panel for their recommendation on the appropriate classification of tissue expanders intended for use in the breast, tissue expanders intended for use in other parts of the body (non-breast use), and accessories for tissue expanders under product code "LCJ."

Appendix A: Literature Search Terms and Filters for Tissue Expanders

Table 11 and Table 12 depict search strategies from PubMed and EMBASE. Search strategies were generated using the device type, and disease of interest along with their synonyms. Search strategies also utilized Boolean operators and medical subject heading [MeSH] terms where necessary.

Table 11: Search Strategy for PubMed (April 12, 2022)

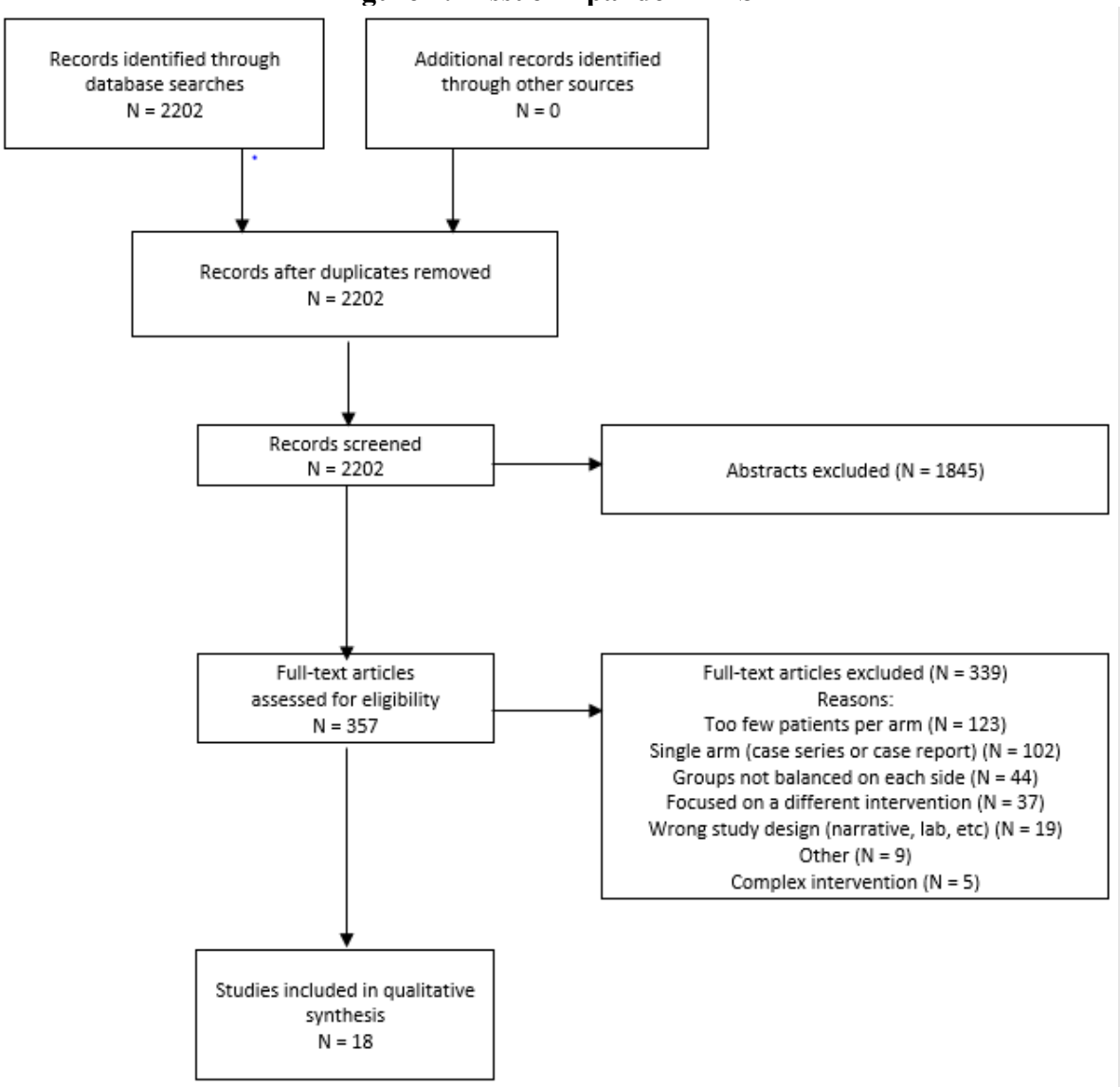
Search Number	Query	Results
#7	#5 NOT #6	274
#6	"case reports"[Publication Type] OR "clinical conference"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "letter"[Publication Type]	4,088,029
#5	#3 AND #4	372
#4	((("2005/04/01"[Date - Publication] : "3000"[Date - Publication])) AND (english[Language])) AND (human)	9,956,291
#3	#1 AND #2	580
#2	"reconstructive surgical procedures"[MeSH Major Topic]	182,114
#1	"tissue expansion devices"[MeSH Major Topic]	995

Table 12: Search Strategy for Embase (April 12, 2022)

Search Number	Query	Results
#6	#1 AND #2 AND 'human' AND [english]/lim NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim)	815
#5	#1 AND #2 AND 'human' AND [english]/lim	971
#4	#1 AND #2 AND 'human'	1,001
#3	#1 AND #2	1,064
#2	'reconstructive surgery'	137,879
#1	('tissue expander'/exp OR 'tissue expander') AND [2005-2022]/py	2,816

Appendix B: Flow Diagram of Systematic Literature Review Search Results

Figure 1: Tissue Expander PRISMA



Although the flowchart above identifies that 18 studies were included in the literature search and subsequent analysis, it was determined afterwards that one (1) study should be excluded from the analysis because it examined tissue expanders used in dentistry, which is a use that FDA has not cleared for tissue expanders. Therefore, in total, 17 studies were reviewed for the purposes of this literature search on tissue expanders.

Appendix C: Summary of Systematic Literature Review Articles for Tissue Expanders

Table 13: Studies Included in the Systematic Literature Review for Tissue Expanders

Study Characteristics	Patient Characteristics	Device Brand/ Manufacturer	Safety Outcomes
Reference: Bae et al. 2022 **Country:** South Korea **Study Design:** Retrospective cohort **Purpose:** To evaluate incidence of rupture of silicone implant following immediate two-stage prosthetic breast reconstruction and investigate potential association of several patient- and operation-related variables with implant rupture **Length of follow-up:** 5 years Median from first stage operation: 53 months Median from second-stage operation: 43 months **Funding Source:** NR	**Patients (N):** 744 patients (797 cases) Micro: 658 cases Macro: 139 cases ADM: 470 cases No ADM: 326 cases **Age mean (SD, range):** 43.6 years (7.4, 18-66) **Sex (% male):** 0 **Diagnosis:** Breast cancer **Inclusion criteria:** Patients with breast cancer who underwent immediate two-staged TE/silicone implant reconstruction following total mastectomy between 2010-2016 and completed both stages **Exclusion criteria:** Patients who underwent one-stage DTI reconstruction, combination methods with implant and autologous flaps together, or delayed reconstruction **Comorbidities, % (n):** Diabetes: NR (8) Hypertension: NR (31)	**Intervention:** Microtextured expander (Siltex) **Comparator:** Macrotextured expander (Biocell)	*Note:* Rates use number of reconstruction cases as denominator. **Device failure:** Implant rupture, n (%): Micro vs. Macro: 19 (2.9) vs. 3 (2.2) HR(Micro=referent): 2.252 (95% CI: 0.605 to 8.382), p=0.226 *Note*: HR calculated via univariate analysis.
Reference: Song et al. 2017 **Country:** South Korea **Study Design:** retrospective chart review **Purpose:** To review the clinical features of cases of implant	**Patients (N):** 771 patients total (832 treated breasts and 1,163 cases of implant-based reconstruction) of which 229 reconstructions were direct-to-implant and 934 reconstructions received tissue expanders **Age median (range):** 45.2 years (age range: 18–83) of patients experiencing a	**Intervention:** TE **Comparator:** DTI **All:** All implants and expanders were placed in the sub-pectoralis	**Definitions:** The definition of cellulitis was based on the criteria published by the CDC and total reconstructive failure was defined as the requirement for complete explantation of the breast prosthesis. **Cellulitis Overall N (%):** Total 58/1163 (5.0%), DTI 26/229 (11.4%), TE 32/934 (3.4%)

infection and investigate the risk factors for breast device salvage failure. **Length of follow-up:** median 46 months (range, 16–65 months) **Funding Source:** NR	postoperative implant infection **Sex (% male):** 0% **Diagnosis:** breast cancer requiring mastectomy followed by reconstruction **Inclusion criteria:** 771 patients who underwent implant-based breast reconstruction between January 2010 and December 2016 were included. **Exclusion criteria:** NR **Comorbidities (% (n):** DM was present in 3/34 patients (8.82%) with cellulitis and in 1/24 patients (4.17%) requiring implant removal; HTN was present in 5/34 (14.7%) with cellulitis and 4/24 patients requiring implant removal (16.7%)	muscle or using ADM as a sling. Interrupted 2-0 Vicryl sutures were used to affix the ADM, moving from the inframammary fold along the inferior breast.	**Cellulitis alone/Salvage rate** Total 34/58 (58.6%), DTI 22/28 (78.6%), TE 12/30 (40.0%); **Cellulitis requiring Implant removal** Total 24 (41.4%), DTI 6/28 (21.4%), TE 18/30 (60.0%), p=0.003 for between group difference, favors DTI. **Implant removal/Explantation after breast implant infection** Explantation after breast implant infection was performed more frequently in patients who underwent TE than in those who underwent DTI: adjusted OR 5.5 (95% CI 1.72 to 17.57, p=0.004), favors DTI.
Reference: Casella et al. 2021 **Country:** Italy **Study Design:** Retrospective cohort **Purpose:** To create a risk-assessment score to safely outline the surgical indication toward prepectoral or submuscular breast reconstruction **Length of follow-up:** Mean: 37.5 months Range: 12-60 months **Funding Source:** NR	**Patients (N):** 352 TE: 240 (68.2%), DTI: 112 (31.8%) **Age mean (range):** 55.9 years (23-80) **Sex (% male):** 0 **Diagnosis:** Confirmed breast cancer or genetic predisposition (i.e., mutation in *BRCA1* or *BRCA2* genes) **Inclusion criteria:** Women ≥18 years undergoing NSM or SSM between January 2014 and December 2018, followed by immediate prepectoral breast reconstruction with TE or DTI assisted by positioning of TCPM (TiLoop Bra, pfm medical) **Exclusion criteria:** NR	**Intervention:** TE (Allergan and Mentor; Contour Profile Expanders) **Comparator:** DTI (Nastrelle 410, Allergan, Inc.; Mentor Breast Implants, Mentor Worldwide)	*Note:* Rates use number of patients as denominator. **Complications, TE vs. DTI (n):** 21 vs. 5 *Note*: Complications caused by infection (1.7%), seroma (2.3%), skin-nipple necrosis (3.1%), and hematoma (1.1%).

	Comorbidities, % (n): Diabetes: 7.4 (26)		
Reference: ElSherif et al. 2021 **Country:** USA **Study Design:** Retrospective review of prospective database **Purpose:** To identify the appropriate prophylactic antibiotic choice for NSM with IBR based on the different microbial species implicated and assess the incidence of SSI according to prosthetic reconstruction type **Length of follow-up:** Median: 1.7 years **Funding Source:** NR	**Patients (N):** 347 patients TE: 259 cases, DTI: 312 cases **Age median:** 48 years TE: 46 years, DTI: 48 years (p=0.007) **Sex (% male):** 0 **Diagnosis:** Breast cancer NSM: 296 patients, Prophylactic NSM: 51 patients **Inclusion criteria:** NSM with IBR between 2010-2019 **Exclusion criteria:** NR **Comorbidities, TE vs. DTI, % (n):** Diabetes: 0 (0) vs. 2 (6), p=0.034	**Intervention:** TE **Comparator:** DTI	*Note:* Rates use number of reconstruction cases as denominator. **Infection, TE vs. DTI:** SSI, n (%): 40 (15) vs. 29 (9), p=0.034* SSI requiring operation, n (%): 25 (10) vs. 12 (4), p=0.008* Early SSI (≤30 days postoperatively), OR: 1.38 (95% CI: 0.62 to 3.08), p=0.42 Late SSI (>30 days postoperatively), OR: 3.8 (95% CI: 1.1 to 13.07), p=0.033*, favoring DTI **Infection, Prophylactic vs. Cancer**: Early SSI, OR: 0.6 (95% CI: 0.28 to 1.3), p=0.2 Late SSI, OR: 1.4 (95% CI: 0.44 to 4.42), p=0.565 **Skin trauma, TE vs. DTI:** Postoperative nipple necrosis (%): 12 vs. 6, p=0.003*
Reference: Lee et al. 2021 **Country:** South Korea **Study Design:** Retrospective review of prospective database; propensity score matched on age, BMI, smoking status, diabetes, hypertension, neoadjuvant chemotherapy, mastectomy specimen weight, mastectomy type, and TE size **Purpose:** To evaluate the outcomes of two-stage prosthetic breast reconstruction using microtextured and macrotextured TEs	**Patients (N):** 1324 Micro: 1109 cases (79.7%), Macro: 282 cases (20.3%) *Propensity score matched, First stage analysis:* Micro: 276 cases, Macro: 276 cases *Propensity score matched, Second stage analysis*: Micro: 195 cases, Macro: 199 cases **Age mean (SD), propensity score matched:** Micro: 45.0 (8.1), Macro: 44.7 (7.7), p=0.672 **Sex (% male):** 0 **Diagnosis:** Breast cancer **Inclusion criteria:** Patients who underwent immediate two-stage subpectoral TE/implant breast reconstruction after total	**Intervention:** Microtextured expander (Siltex) **Comparator:** Macrotextured expander (Biocell)	*Note:* Rates use number of reconstruction cases as denominator. ***Post-First Stage Operation, Micro vs. Macro, n (%)*** **Infection:** Overall infection: 6 (2.2) vs. 5 (1.8), p=0.761 Early onset (≤1 month) infection: 5 (1.8) vs. 2 (0.7), p=0.254 Delayed onset (>1 month) infection: 1 (0.4) vs. 3 (1.1), p=0.316 **Skin trauma:** Seroma: 11 (4.0) vs. 1 (0.4), p=0.004* OR: 0.050 (95% CI: 0.005 to 0.523), p=0.012*, favoring Macro Hematoma: 6 (2.2) vs. 1 (0.4), p=0.057 OR: 0.122 (95% CI: 0.012 to 1.261), p=0.078, favoring Macro

Length of follow-up: Mean: 40.0 months Range: 13-68 months **Funding Source:** NR	mastectomy between January 2014 and December 2018 **Exclusion criteria:** Delayed TE insertion, combined autologous tissue and TE **Comorbidities, propensity score matched, Micro vs. Macro, % (n):** Diabetes: 1.4 (4) vs. 1.1 (3), p=0.704 Hypertension: 6.5 (18) vs. 6.2 (17), p=0.861		Mastectomy flap necrosis: 19 (6.9) vs. 12 (4.3), p=0.196 Nipple necrosis: 4 (1.4) vs. 3 (1.1), p=0.704 Wound dehiscence: 6 (2.2) vs. 7 (2.5), p=0.779 **Reoperation:** Revision surgery: 20 (7.2) vs. 11 (4.0), p=0.096 **Explantation:** 4 (1.4) vs. 2 (0.7), p=0.412 **Other:** Displacement: 24 (9.8) vs. 21 (8.4), p=0.609 Prolonged drain duration: 96 (34.8) vs. 37 (13.4), p<0.001* OR: 0.215 (95% CI: 0.121 to 0.380), p<0.001*, favoring Macro ***Post-Second Stage Operation, Micro vs. Macro, n (%)*** **Infection:** Overall infection: 1 (0.5) vs. 1 (0.5), p=0.989 **Skin trauma:** Seroma: 3 (1.5) vs. 0 (0), p=0.079 Hematoma: 2 (1.0) vs. 2 (1.0), p=0.984 Severe capsular contracture: 9 (4.6) vs. 17 (8.5), p=0.116 OR: 3.012 (95% CI: 1.169 to 7.759), p=0.022*, favoring Micro *Note*: OR calculated using multivariate analysis **Reoperation:** Implant exchange: 4 (2.1) vs. 3 (1.5), p=0.683 Implant removal: 1 (0.5) vs. 2 (1.0), p=0.574 **Other:** Implant malposition: 6 (3.1) vs. 6 (4.0), p=0.613
Reference: Broyles et al. 2020 **Country:** USA **Study Design:** Retrospective cohort	**Patients (N):** 208 TE: 101, DTI: 107 **Age mean (SD):** 50.5 years (10) **Sex (% male):** 0	**Intervention:** TE **Comparator:** DTI	*Note:* Rates use number of patients as denominator. **Other, TE vs. DTI:** Minor complications, OR: 2.51 (95% CI: 1.39 to 4.53), p=0.002*, favoring DTI

Purpose: To investigate the relationship between frailty and adverse outcomes in patients who underwent radiation followed by autologous, abdominally based breast reconstruction using sarcopenia as a proxy for frailty **Length of follow-up:** Mean (SD): 50 months (4) **Funding Source:** NR	**Diagnosis:** Breast cancer **Inclusion criteria:** Female patients ≥18 years who underwent delayed abdominally based free flap breast reconstruction following postmastectomy radiation therapy from 2007-2013 at the MD Anderson Cancer Center **Exclusion criteria:** Patients who did not have a preoperative CT scan of the abdomen and pelvis up to 6 months before microvascular free flap reconstruction, <1 year follow-up, surgery outside the study period of January 2007 to January 2013 **Comorbidities, % (n):** Cerebrovascular disease: 1.92 (4) CHF: 0.96 (2) Diabetes: 2.88 (6) Hypertension: 20.7 (43) Peripheral vascular disease: 1.44 (3) Rheumatologic disease: 2.40 (5)		Major complications, OR: 2.56 (95% CI: 1.31 to 5.02), p=0.015*, favoring DTI *Note:* OR for minor complications calculated via multivariate analysis adjusted for smoking status, hypertension, sarcopenia, and obesity. OR for major complications calculated via multivariate analysis adjusted for sarcopenia, obesity, and chemotherapy. *Note:* Minor complications defined as not requiring readmission or reoperation (e.g., fat necrosis, donor or recipient site seroma, site infection treated with oral antibiotics, wound-healing issue, hematoma, any incisional dehiscence that was managed conservatively). Major complications defined as requiring readmission and/or surgical intervention (e.g., total flap loss, donor or recipient site seroma or hematoma that required operative evacuation, flap thrombosis requiring operative interrogation, wound infection requiring IV antibiotics, return to operative room for any wound-healing issue).
Reference: Chiu et al. 2020 **Country:** USA **Study Design:** Retrospective chart review; propensity score matched on age, BMI, smoking history, hypertension, diabetes, mastectomy type, laterality of breast reconstruction, and history of radiotherapy **Purpose:** To perform propensity matching between smooth and textured TE cohorts to provide insight into the	**Patients (N): 282** Textured: 141 breasts, Smooth: 141 breasts **Age mean (SD):** Textured: 46.54 (9.89), Smooth: 45.85 (11.23), p=0.585 **Sex (% male):** 0 **Diagnosis:** NR **Inclusion criteria:** Patients who underwent immediate two-stage subpectoral TE breast reconstruction after mastectomy from August 2013 to May 2018 **Exclusion criteria:** NR	**Intervention:** Textured TE (Allergan MTX) **Comparator:** Smooth TE (Mentor Artoura)	*Note:* Rates use number of breasts as denominator. **Skin trauma, Textured vs. Smooth, n (%):** Mastectomy flap necrosis: 12 (8.51) vs. 8 (5.67), p=0.353 Seroma: 1 (0.71) vs. 7 (4.96), p=0.031* Exposure/dehiscence: 5 (3.55) vs. 5 (3.55), p=1.000 **Infection, Textured vs. Smooth, n (%):** Major infection: 3 (2.13) vs. 2 (1.42), p=0.652 Minor infection: 5 (3.55) vs. 0 (0), p=0.024* *Note*: Major infection defined as requiring IV antibiotics or expander removal. Minor infection

impact of expander texture on breast reconstruction outcomes **Length of follow-up:** 90 days **Funding Source:** None	**Comorbidities, Textured vs. Smooth, % (n):** Hypertension: 16 (11.35) vs. 20 (14.18), p=0.477) Diabetes: 6 (4.26) vs. 7 (4.96), p=0.780		defined as requiring oral antibiotics only. **Explantation, Textured vs. Smooth, n (%):** 5 (3.55) vs. 7 (4.96), p=0.555
Reference: Casella et al. 2019 **Country:** Italy **Study Design:** Retrospective chart review **Purpose:** To compare risk factors and outcomes between patients undergoing DTI and two-stage TE prepectoral breast reconstruction **Length of follow-up:** Mean: 38 months **Funding Source:** None	**Patients (N):** 397 TE: 187 (237 breasts), DTI: 210 (284 breasts) **Age mean (SD, range):** 55.8 years (13.6, 23-80) TE: 55.5 years (NR, 29-80), DTI: 56.1 years (NR, 23-79), p=0.64 **Sex (% male):** 0 **Diagnosis, TE vs. DTI, n (%):** Breast cancer: NR *BRCA* mutation carriers: 37 (17.6) vs. 58 (27.6), p=0.07 **Inclusion criteria:** Women ≥18 years who underwent SSM or NSM followed by prepectoral breast reconstruction assisted by TCPM synthetic mesh (TiLOOP Bra) between January 2012 and December 2016, confirmed breast cancer or genetic predisposition, grade I-II ptosis, minimum 1 year follow-up from reconstruction **Exclusion criteria:** BMI ≥35 kg/m^2, pregnancy, breast size larger than C cup, delayed breast reconstruction **Comorbidities, TE vs. DTI, % (n):** Presence of comorbidities: 8 (15) vs. 8.6 (18), p=0.84	**Intervention:** TE **Comparator:** DTI	*Note:* Rates use number of breasts as denominator. **Reoperation, TE vs. DTI, n (%):** Surgical complications requiring second operation: 16 (6.7) vs. 14 (4.9), p=0.37 **Skin trauma, TE vs. DTI, n (%):** Skin-nipple necrosis: 2 (0.8) vs. 3 (1.1) Wound dehiscence: 4 (1.7) vs. 3 (1.1) Seroma: 3 (1.2) vs. 2 (0.7) Hematoma: 0 (0) vs. 1 (0.3) Severe capsular contracture: 9 (3.8) vs. 10 (3.5) *Note*: Severe capsular contracture defined as Baker Scale grade III and IV. **Infection, TE vs. DTI, n (%):** 7 (3.0) vs. 5 (1.8) **Explantation, TE vs. DTI, n (%):** Implant removal: 9 (3.8) vs. 7 (2.5), p=0.38 **Other, TE vs. DTI, n (%):** Implant dystopia: 2 (0.8) vs. 2 (0.7) Rippling: 28 (11.8) vs. 37 (13)
Reference: Bennett et al. 2018	**Patients (N):** 2343 TE: 1525 (65.1%), DTI: 112 (4.8%); flap surgery: 706 (30.1%)	**Intervention:** TE	*Note:* Rates use number of patients as denominator. **Other, TE vs. DTI, n (%):**

Country: USA, Canada **Study Design:** Longitudinal, multicenter (11 sites), prospective cohort **Purpose:** To assess 2-year complication rates across common techniques for postmastectomy reconstruction (TE, DTI, autologous) in a multicenter patient population **Length of follow-up:** 2 years **Funding Source:** NCI grant R01CA152192, NIDCR grant 1F32DE027604-01	**Age mean (SD):** TE: 48.4 years (10.3), DTI: 48.2 years (12.1) **Sex (% male):** 0 **Diagnosis:** Breast cancer **Inclusion criteria:** Women ≥18 years, first-time breast reconstruction after mastectomy for cancer treatment or prophylaxis, undergoing DTI, TE, LD flap, pTRAM flap, fTRAM flap, DIEP flap, or SIEA flap procedures **Exclusion criteria:** Mixed reconstructive timing (1 side immediate, 1 side delayed), mixed procedure types (1 side implant, 1 side autologous), cross-over reconstructions (delayed-immediate reconstruction beginning with implant techniques with an autologous second stage or implant converted to autologous) **Comorbidities, TE vs. DTI, % (n):** Diabetes: 46 (3.0) vs. 3 (2.7), p<0.001	**Comparator:** DTI	Any complication: 406 (26.6) vs. 35 (31.3) OR: 1.08 (95% CI: 0.65 to 1.77), p=0.78 **Reoperation, TE vs. DTI, n (%):** Reoperative complication: 237 (15.5) vs. 21 (18.8) OR: 1.06 (95% CI: 0.56 to 1.99), p=0.87 **Device failure, TE vs. DTI, n (%):** Reconstructive failure: 108 (7.1) vs. 8 (7.1) **Infection, TE vs. DTI, n (%):** Wound infection: 159 (10.4) vs. 17 (15.2) OR: 1.70 (95% CI: 0.91 to 3.18), p=0.10 *Note*: Complication defined as an adverse, postoperative, surgery-related event that required additional treatment. Wound infection defined by CDC criteria: (1) presence of purulent drainage, (2) positive aseptically obtained culture result, (3) peri-incisional erythema and incision opened by the surgeon, or (4) physician diagnosis of infection for which antibiotics were prescribed. *Note*: ORs calculated via mixed-effects regression model with covariates age, BMI, race, ethnicity, income, education, marital status, employment, diabetes, smoking, timing of reconstruction, laterality, lymph node management, indication for mastectomy, radiotherapy, and chemotherapy.
Reference: Casella et al. 2017 **Country:** Italy **Study Design:** Multicenter (15 sites), retrospective cohort (2009-2011) and	**Patients (N):** 913 TE: 650 cases (64.6%), DTI: 278 cases (27.6%) **Age mean (SD):** NR *Age distribution, n (%)*: <25 years: 2 (0.2) 25-39 years: 178 (19.5) 40-54 years: 577 (63.2) 55-69 years: 147 (16.1)	**Intervention:** TE **Comparator:** DTI	*Note:* Rates use number of reconstruction cases as denominator. **Device failure, TE vs. DTI, n (%):** Reconstruction failure: 17 (2.7) vs. 6 (2.3) OR: 1.10 (95% CI: 0.36 to 3.41), p=0.858

prospective cohort (2011-2014) **Purpose:** To perform a further in-depth analysis of trends and outcomes of breast reconstruction following NSM in the Italian National Database on NSM **Length of follow-up:** 1 year **Funding Source:** "La corsa della speranza", Montecatini Terme, Pistoia; Institutional University of Florence funds for Scientific Research projects **Notes:** Some demographic data came from a second publication	>69 years: 9 (1.0) **Sex (% male):** 0 **Diagnosis:** Breast cancer **Inclusion criteria:** NSM performed between January 2009 and December 2014, sites with ≥15 cases entered in the registry, patients with an updated reconstructive follow-up until 1 year from NSM **Exclusion criteria:** NR **Comorbidities, % (n):** Diabetes Type I: 0.3 (3) Diabetes Type II: 0.3 (3)		*Note*: Failure defined as prosthesis removal due to complications within 1 year from NSM. OR calculated via multivariate analysis that included covariates age, smoke, diabetes, oncological stage, neoadjuvant chemotherapy, and preoperative radiation.
Reference: Corban et al. 2017 **Country:** Authors from Canada and Saudi Arabia **Study Design:** Systematic review **Purpose:** To determine the complications associated with DTI and two-step TE breast reconstruction following Wise pattern SSM **Length of follow-up:** NR **Funding Source:** NR	**Patients (N):** 561 reconstructions TE: 128 reconstructions, DTI: 433 reconstructions **Age mean (SD):** TE: 52.5 years (NR), DTI: 48.7 years (NR) **Sex (% male):** 0 **Diagnosis:** NR **Inclusion criteria:** Articles published since 1991 in peer-reviewed journals involving human subjects; written in English; described SSM with immediate or delayed reconstruction; reported on outcomes from Type IV, Wise pattern, or Inverted T SSM with one- or two-step reconstruction; stratified surgical outcomes by type and timing of reconstructions	**Intervention:** TE **Comparator:** DTI	*Note*: Rates use number of reconstructions as denominator. **Other, TE vs. DTI, pooled n (%):** Overall complications: 26 (20.3) vs. 131 (30.3) *Note*: Includes minor/major complications Neo-nipple graft loss: NR vs. 7 (1.62) Other complications requiring reevaluation: 4 (3.12) vs. NR Contour deformity: NR vs. 2 (0.46) **Skin trauma, TE vs. DTI, pooled n (%):** Skin flap necrosis: 6 (4.69) vs. 42 (9.69) *Note*: Includes partial/full thickness necrosis, minor/major necrosis, extensive necrosis, and partial necrosis of nipple grafts. Delayed wound healing: 1 (0.78) vs. 12 (3.00)

	Exclusion criteria: Case series <5 patients, case reports **Comorbidities, % (n):** NR		Seroma: 6 (4.69) vs. 5 (1.15) Hematoma: 1 (0.78) vs. 4 (0.92) Contracture: NR vs. 17 (3.93) Nipple scaring: NR vs. 10 (2.31) Epidermolysis: NR vs. 10 (2.31) **Infection, TE vs. DTI, pooled n (%):** 5 (3.91) vs. 11 (2.25) **Explantation, TE vs. DTI, pooled n (%):** Implant extrusion: NR vs. 3 (0.69) Expander extrusion: 1 (0.78) vs. NR Implant loss: NR vs. 7 (1.62)
Reference: Frey et al. 2017 **Country:** USA **Study Design:** Retrospective cohort **Purpose:** To compare outcomes between different techniques for prosthetic and autologous tissue breast reconstruction to better define and optimize patient-specific outcomes by type of reconstruction (TE, DTI, autologous) after NSM **Length of follow-up:** TE, mean: 41.7 months DTI, mean: 25.7 months **Funding Source:** NR	**Patients (N):** 1028 TE: 533 (51.8%), DTI: 232 (22.6%); autologous 263 (25.6%) **Age mean (SD):** TE: 46.48 (NR), DTI: 47.29 (NR), p=0.306 **Sex (% male):** 0 **Diagnosis:** Breast cancer **Inclusion criteria:** Patients undergoing NSM from 2006 to June 2016 followed by TE, DTI, or autologous breast reconstruction **Exclusion criteria:** LD flap reconstruction, combined implant-based and autologous reconstruction, solely autologous fat transfer for breast reconstruction **Comorbidities, TE vs. DTI (%):** Diabetes: 2.4 vs. 2.6, p=0.853	**Intervention:** TE **Comparator:** DTI	*Note:* Rates use number of patients as denominator. **Skin trauma, TE vs. DTI (%):** Partial nipple necrosis: 5.8 vs. 7.8, p=0.2018 Complete nipple necrosis: 1.3 vs. 3.9, p=0.0005* Major mastectomy flap necrosis: 1.9 vs. 6.5, p<0.0001* Minor mastectomy flap necrosis: 7.7 vs. 12.9, p=0.0028* Seroma: 1.1 vs. 0.4, p=0.3286 Hematoma: 1.9 vs. 1.7, p=0.8445 Minor cellulitis: 7.1 vs. NR, p=0.0006* (TE had significantly more minor cellulitis) **Infection, TE vs. DTI (%):** Major infection: 1.1 vs. 1.7, p=0.3668 Minor infection: 7.1 vs. 3.0, p=0.0155* **Explantation, TE vs. DTI (%):** 2.3 vs. 3.4, p=0.141 **Device failure, TE vs. DTI (%):** Implant failure: 2.4 vs. 3.9, p=0.2208 *Note*: Major complications defined as requiring IV antibiotics. Minor complications defined as requiring only oral antibiotics.
Reference: Ilonzo et al. 2017 **Country:** USA	**Patients (N):** 67,450 TE: 18,143; DTI: 2719; mastectomy without reconstruction: 42,109; flap: 4,456	**Intervention:** TE **Comparator:** DTI	*Note:* Rates use number of patients as denominator. **Infection, TE vs. DTI (%):**

Study Design: Retrospective cohort **Purpose:** To assess trends in type of reconstruction performed after mastectomy, evaluate independent predictors for electing reconstruction, and compare immediate postoperative outcomes between reconstruction types (TE, DTI, LD, TRAM, free flap) from the NSQIP database **Length of follow-up:** 30 days **Funding Source:** NR	**Age mean (SD):** TE: 51.46 (NR), DTI: 51.99 (NR) **Sex (% male):** 0 **Diagnosis:** Breast cancer **Inclusion criteria:** Patients who underwent mastectomy for breast malignancy between 2005-2014 followed by implant or autologous breast reconstruction **Exclusion criteria:** NR **Comorbidities, TE vs. DTI (%):** Hypertension: 23.79 vs. 25.12 Coronary artery disease: 0.54 vs. 0.59 Diabetes: 5.09 vs. 4.27 Neurologic deficit: 0.17 vs. 0.33 *Note*: Neurologic deficit defined as any patient with history of CVA with neurologic asymmetry, hemiplegia, quadriplegia, or paraplegia.		Wound complications: 3.89 vs. 4.38, p=0.18 TE, OR: 1.02 (95% CI: 0.72 to 1.44), p>0.05 DTI, OR: 1.18 (95% CI: 0.83 to 1.68), p<0.05* Infection complications: 0.7 vs. 0.82, p=0.46 *Note*: ORs calculated via multivariate logistic regression with covariates gender, race, age, smoking status, hypertension, ASA class, comorbidities, preoperative chemotherapy or radiation, history and type of reconstruction, and BMI. **Other, TE vs. DTI (%)**: Bleeding complications: 0.64 vs. 0.76, p=0.45 *Note*: Wound complications defined as occurrence of superficial or deep organ space infection or wound dehiscence. Infections included pneumonia or UTI. Major bleeding complications defined as those requiring transfusion.
Reference: Sinha et al. 2017 **Country:** USA, Canada **Study Design:** Post hoc analysis of prospective multicenter (11 sites) cohort study **Purpose:** To evaluate early and late SSI in immediate implant-based reconstruction and identify predictors within the MROC study **Length of follow-up:** TE: 2 years, DTI: 1 year	**Patients (N):** 1024 TE 1st Stage: 1491 breasts; TE 2nd Stage: 1266 breasts; DTI: 171 breasts **Age mean (SD):** 48.42 years (10.57) **Sex (% male):** 0 **Diagnosis:** Breast cancer **Inclusion criteria:** Women 18 years or older undergoing first-time unilateral or bilateral mastectomy breast reconstruction **Exclusion criteria:** NR **Comorbidities, % (n):** Diabetes: 3.52 (36)	**Intervention:** TE **Comparator:** DTI	*Note:* Rates use number of breasts as denominator. **Infection, n (%):** Overall SSI, TE vs. DTI: 114 (7.7) vs. 17 (9.9) Early SSI (≤30 days postoperatively), TE 1st Stage vs. TE 2nd Stage vs. DTI: 43 (2.9) vs. 9 (0.7) vs. 9 (5.3) *Major Early SSI (%):* 1.7 vs. 0.2 vs. 3.5 *Minor Early SSI (%):* 1.2 vs. 0.5 vs. 1.8 Late SSI (31-365 days postoperatively), TE vs. DTI: 65 (56.0) vs. 8 (47.1) OR: 1.02 (95% CI: 0.411 to 2.550), p=0.959, no difference between TE and DTI *TE 1st Stage vs. TE 2nd Stage vs. DTI:* 43 (2.8) vs. 22 (1.8) vs. 8 (4.7)

Funding Source: NCI grant 1R01CA152192			*Major Late SSI (%):* 1.7 vs. 1.2 vs. 2.9 *Minor Late SSI (%):* 1.1 vs. 0.6 vs. 1.8 Overall major infection, TE 1st Stage vs. DTI, n (%): 51 (3.4) vs. 11 (6.4) Overall minor infection, TE 1st Stage vs. DTI, n (%): 35 (2.3) vs. 6 (3.5) *Note:* Minor infection defined as requiring oral antibiotics only. Major infection defined as requiring hospitalization and/or surgical treatment. **Explantation, TE 1st Stage vs. TE 2nd Stage vs. DTI, n (%):** 36 (42.4) vs. 7 (22.6) 4 (23.5) *Note:* ORs calculated via mixed-effects logistic regression with covariates BMI, reconstructive procedure type, indication for mastectomy, ADM usage, smoking status, and radiation therapy.
Reference: Basta et al. 2015 **Country:** Authors from USA **Study Design:** Systematic review and head-to-head meta-analysis **Purpose:** To evaluate the safety and efficacy of using DTI vs. conventional two-stage reconstruction (TE/implant) **Length of follow-up:** Mean (SD): 40.8 months (26.8) **Funding Source:** Department of Surgery at the Hospital of the University of Pennsylvania,	**Patients (N):** 5216 cases TE: 2417 cases, DTI: 2799 cases **Age mean (SD):** 47.2 (1.0) **Sex (% male):** 0 **Diagnosis:** Breast cancer **Inclusion criteria:** Articles published between 2000-2015 involving immediate prosthetic-based breast reconstruction for cancer management, both a two-stage TE and DTI technique used, reconstructive techniques similar for DTI and TE groups, study reported relevant outcomes for each group, published in English language **Exclusion criteria:** Limited to single case reports or review of the literature, did	**Intervention:** TE **Comparator:** DTI	*Note:* Rates use number of cases as denominator. **Infection, TE vs. DTI, pooled incidence % (95% CI):** Implant infection: 7.4 (2.7 to 12.1) vs. 7.8 (3.7 to 12.0) OR: 1.08 (0.68 to 1.72), p=0.74 **Skin trauma, TE vs. DTI, pooled incidence % (95% CI):** Seroma: 7.1 (3.1 to 11.1) vs. 6.8 (2.5 to 11.0) OR: 0.95 (95% CI: 0.57 to 1.60), p=0.85 Flap necrosis: 6.7 (2.7 to 10.6) vs. 8.6 (1.9 to 15.4) OR: 1.43 (95% CI: 1.09 to 1.86), p=0.01, favoring TE Contracture: 13.8 (0.3 to 27.2) vs. 13.5 (-5.1 to 32.3) OR: 0.90 (95% CI: 0.44 to 1.85), p=0.77 **Reoperation, TE vs. DTI, pooled incidence % (95% CI):** 14.1 (6.2 to 22.1) vs. 17.9 (5.0 to 30.8)

Perelman School of Medicine at the University of Pennsylvania	not report sufficient data for both DTI and TE cohorts, prosthesis placed in conjunction with autologous tissue flap, did not meet Inclusion criteria specified above **Comorbidities, % (n):** NR		OR: 1.25 (95% CI: 1.02 to 1.53), p=0.04, favoring TE **Explantation, TE vs. DTI, pooled incidence % (95% CI):** 8.7 (2.0 to 15.4) vs. 14.4 (7.3 to 21.4) OR: 1.87 (95% CI: 1.05 to 3.34), p=0.04, favoring TE
Reference: Fischer et al. 2015 **Country:** USA **Study Design:** Retrospective cohort; review of 2007-2012 AHRQ HCUP inpatient and ambulatory surgery databases for California, Florida, Nebraska, and New York **Purpose:** To compare short- and long-term outcomes after TE, autologous, and DTI breast reconstruction **Length of follow-up:** 90 days for complications, 3 years for reoperation **Funding Source:** NR	**Patients (N):** 15,154 TE: 10,690 (70.5%), DTI: 1717 (11.3%), Autologous: 2,747 (18.2%) **Age mean (SD):** TE: 51.8 years (10.7), DTI: 52.7 years (11.4) **Sex (% male):** 0 **Diagnosis, TE vs. DTI, N (%):** In situ breast cancer: 2155 (20.2) vs. 395 (23.0) Invasive node (+): 2258 (21.1) vs. 293 (17.1) Invasive node (-): 6277 (58.7) vs. 1029 (59.9) **Inclusion criteria:** Women ≥18 years who underwent mastectomy for breast cancer with concurrent breast reconstruction between October 2007 and December 2009 **Exclusion criteria:** Discharges with concurrent coding for both lumpectomy and mastectomy; patients with known metastatic disease and where discharge disposition recorded as unknown or death; died in hospital during 3-year follow-up period; undergone lumpectomy, mastectomy, or plastic and reconstructive breast procedures in year before study period **Comorbidities, TE vs. DTI, % (n):**	**Intervention:** TE **Comparator:** DTI	*Note:* Complication rates use number of patients as denominator. Secondary breast procedures use number of discharges or number of patients as denominator. **Other, TE vs. DTI:** Complications requiring hospitalization: 6.5% vs. 6.6%, p<0.001* OR: 1.03 (95% CI: 0.84 to 1.27) *Note:* Complications include inpatient diagnosis of pulmonary failure, pneumonia, MI, DVT or PE, acute renal failure, postoperative hemorrhage, SSI, and GI bleeding. *Note*: OR adjusted for age, race, private insurance status, inpatient versus ambulatory procedure, initial diagnosis, the presence of cardiovascular diseases other than hypertension, COPD, diabetes, hypothyroidism, mental health diagnoses, obesity, and smoking status, and whether the initial procedure was bilateral, if a concurrent axillary node procedure or balancing procedure was performed. **Reoperation, TE vs. DTI:** Additional breast procedures, n per 1000 discharges (95% CI): 2021.0 (1994.2 to 2048.1) vs. 1425.7 (1370.4 to 1483.4), p<0.001* IRR: 0.74 (95% CI: 0.70 to 0.78), p<0.001*, favoring DTI *≥1 additional breast procedure*: 76.2% vs. 56.2% *≥3 additional breast procedures*: 35.8% vs. 23.2%

	Elixhauser comorbidity algorithm: None: 11.0 (1175) vs. 13.2 (227) 1-2: 69.3 (7407) vs. 70.1 (1203) ≥3: 19.7 (2108) vs. 16.7 (287)		Procedures for new/ongoing disease: 28.6% vs. 23.7%, p<0.001* Unplanned revisions: 59.2% vs. 45.9%, p<0.001* Autologous reconstruction: 6.8% vs. 4.8%, p<0.001* *Note:* Procedures for new/ongoing disease include mastectomy, lumpectomy, and biopsy. Unplanned revisions include implant removal, revision, or exchange; TE removal without replacement; reconstruction with different modality; and revision of reconstruction breast without further specification. Autologous reconstruction defined as conversion to autologous implant. **Explantation TE vs. DTI:** Implant or expander removal (not exchange): 24.6% vs. 21.1%, p<0.001*
Reference: Davila et al. 2013 **Country:** USA **Study Design:** Retrospective review of NSQIP database (258 participating sites) **Purpose:** To investigate 30-day postoperative complications in patients who underwent two-stage TE placement or one-stage permanent implant placement **Length of follow-up:** 30 days **Funding Source:** NR	**Patients (N):** 10,561 TE: 9033 (85.5%), DTI: 1528 (14.5%) **Age mean (SD):** TE: 50.9 (10.5), DTI: 50.8 (10.6), p=0.67 **Sex (% male):** 0 **Diagnosis:** NR **Inclusion criteria:** Women who underwent immediate TE or DTI following mastectomy from 2006-2010 **Exclusion criteria:** Male or unknown gender patients, concomitant flap reconstruction with TE or implant placement, expander and implant placed simultaneously, no concurrent mastectomy **Comorbidities, TE vs. DTI, % (n):** Diabetes: 4.8 (433) vs. 3.7 (57), p=0.07	**Intervention:** TE **Comparator:** DTI	*Note:* Rates use number of patients as denominator. **Other, TE vs. DTI, n (%):** Total complications: 485 (5.4) vs. 104 (6.8), p=0.02* OR: 1.28 (95% CI: 1.02 to 1.60), p=0.03*, favoring TE Major medical complications: 142 (1.6) vs. 27 (1.8), p=0.57 OR: 1.07 (95% CI: 0.70 to 1.63), p=0.76, favoring TE **Infection, TE vs. DTI, n (%):** Total SSI: 309 (3.4) vs. 59 (3.9), p=0.39 OR: 1.11 (95% CI: 0.83 to 1.49), p=0.48 *Superficial SSI:* 142 (1.6) vs. 25 (1.6), p=0.85 OR: 0.98 (0.63 to 1.53), p=0.93 *Deep SSI*: 101 (1.1) vs. 19 (1.2), p=0.70 OR: 1.14 (95% CI: 0.69 to 1.87), p=0.62 *Organ/space SSI:* 71 (0.8) vs. 16 (1.0), p=0.30 OR: 1.34 (95% CI: 0.77 to 2.31), p=0.30

	Hypertension: 23.0 (2082) vs. 22.3 (340), p=0.49 COPD: 0.8 (71) vs. 1.3 (20), p=0.04 CHF: 0.0 (4) vs. 0.1 (1), p=0.54 Peripheral vascular disease: 0.1 (10) vs. 0.0 (0), p=0.38 Bleeding disorders: 0.7 (61) vs. 0.5 (8), p=0.61 Disseminated cancer: 0.6 (58) vs. 1.0 (15), p=0.14		**Skin trauma, TE vs. DTI, n (%):** Wound disruption: 40 (0.4) vs. 12 (0.8), p=0.08 OR: 1.85 (95% CI: 0.96 to 3.54), p=0.07 **Device failure, TE vs. DTI, n (%):** Prosthesis failure: 76 (0.8) vs. 21 (1.4), p=0.04* OR: 1.71 (95% CI: 1.05 to 2.79), p=0.03*, favoring TE **Reoperation (within 30 days), TE vs. DTI, n (%):** 626 (6.9) vs. 115 (7.5), p=0.40 OR: 1.10 (95% CI: 0.89 to 1.35), p=0.38 *Note*: Superficial SSI defined as infection of the skin and subcutaneous tissue. Deep SSI defined as infection of musculo-fascial layers. Organ/space SSI defined as infection of the deeper tissues. Prosthesis failure defined as mechanical failure or removal of prosthesis requiring return to the operating room. Major medical complication defined as all other complications except for patients requiring reoperation within 30 days and included pneumonia, unplanned intubation, PE, ventilator requirement >48 hours, progressive renal insufficiency, acute renal failure, UTI, peripheral nerve injury, stroke, coma cardiac arrest, MI, transfusion requirement, DVT, sepsis, and septic shock.

Appendix D: Medical Device Report (MDR) Information on Tissue Expanders

Appendix D includes additional adverse event information from MDRs reported for tissue expanders.

Table 14 provides additional information on the BII MDRs that were diagnosed after tissue expander use in the breast.

Table 14: MDRs reporting a diagnosis of BII after tissue expander use

MDR #	Implanted Devices	Implantation	Explantation	Time frame
1645337-2018-03282	Tissue Expander	3,17,2004	Unknown	Unknown
	Saline Implants	Unknown	10,27,2021	Unknown
1645337-2021-13775	Tissue Expanders	Unknown	Unknown	Unknown
1645337-2021-13776	Tissue Expanders	Unknown	Unknown	Unknown
MW5106428	Textured Tissue Expander	12,09,2015	5,17,2016	6 months
	Smooth Breast Implant	5,17,2016	2019	3 years
	Smooth Breast Implant	2019	Unknown	Unknown
MW5023525	Unknown	5,01,2004	Unknown	Unknown
	Gel Implants	Unknown	Unknown	Unknown
MW5088610	Tissue Expander	2,23,2017	Unknown	Unknown
	Gel Breast Implant	Unknown	Unknown	Unknown

	Gel Breast Implant	Unknown	Unknown	Unknown
MW5082063	Tissue expanders	11,02,2005	Unknown	Unknown
	Breast Implant	Unknown	Unknown	Unknown
1645337-2021-09306	Tissue Expander	Unknown	Unknown	Unknown
1645337-2019-09214	Unknown	5,04,2017	7,05,2017	2 months
	Unknown	10,01,2017	Unknown	Unknown
MW5089395	Textured Tissue Expander	5,15,2003	Unknown	Unknown
	Smooth Breast Implant	Unknown	6,18,2019	Unknown
1645337-2020-02142	Unknown	6,14,2017	Unknown	Unknown
MW5088802	Textured Tissue Expander	1,23,2019	Unknown	Unknown
2024601-1999-00089	Gel filled Breast Implant	7,19,1979	5,06,1991	12 years
1645337-2020-09960	Unknown	3,05,2020	7/1/202	4 months
MW5063982	Unknown	9,15,2014	12,11,2015	3 months
9617229-2018-07860	Tissue Expander	9,08,2015	2,18,2016	5 months
MW5088386	Unknown	Unknown	Unknown	Unknown
MW5092144	Unknown	10,01,2018	1,08,2020	15 months
9617229-2020-01100	Tissue Expander	7,15,2019	Unknown	Unknown
9617229-2018-09007	Unknown	6,12,2013	12,05,2013	6 months
1645337-2019-09413	Unknown	Unknown	Unknown	Unknown
		5,28,2015	Unknown	Unknown

	Gel Breast Implants			
1645337-2019-17580	Textured Tissue Expander	10,27,2001	Unknown	Unknown
	Breast Implants	Unknown	5,30,2014	Unknown
9617229-2020-03615	Smooth Tissue Expander	5,02,2019	6,17,2019	1 month
1645337-2020-05655	Unknown	Unknown	4,18,2017	Unknown
	Gel Breast Implant	4,18,2017	unknown	Unknown
MW5087279	textured	2007	Unknown	Unknown
	textured	Unknown	2012	Unknown
MW5090623	Unknown	7,10,2014	Unknown	Unknown
	Unknown	Unknown	Unknown	Unknown
1645337-2020-13170	Unknown	4,30,2019	9,01,2020	17 months
MW5080601	Unknown	6,12,2013	12,05,2013	6 months
	Silicone Breast Implant	12,05,2013	Unknown	Unknown
9617229-2021-52645	Unknown	1,05,2015	2,19,2016	13 months
1645337-2020-16510	Unknown	4,30,2019	9,01,2020	17 months

Table 15 provides additional information on the BIA-ALCL MDRs that were diagnosed after tissue expander use in the breast.

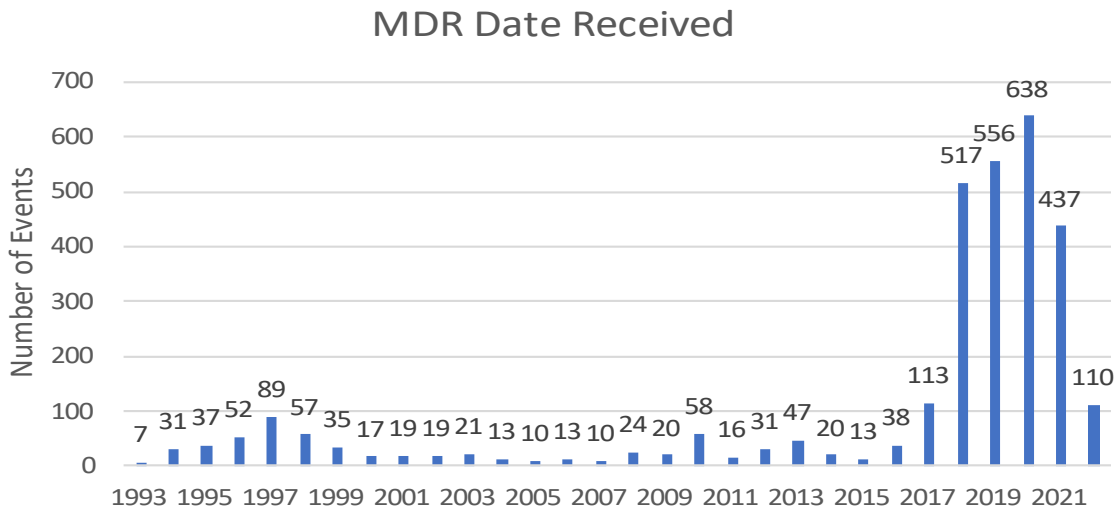
Table 15: MDRs reporting a diagnosis of BIA-ALCL after tissue expander use

MDR number	Tissue Expander Info	Implanted Devices	Implantation date	Explantation date	Implant Duration	BIA-ALCL Diagnosis
9617229-2021-57504	TEXTURED EXPANDER	TISSUE EXPANDER	5/5/2015	9/10/2015	4 mos	5/4/2020

		BREAST IMPLANT	9/10/2015	5/18/2020	5 yrs	
9617229-2022-02065	TEXTURED EXPANDER	TISSUE EXPANDER	5/24/2001	9/5/2001	4 mos	4/23/2019
		BREAST IMPLANT	9/5/2001	5/04/2010	9 yrs.	
		BREAST IMPLANT	5/4/2010	11/21/2012	2 yrs.	
		BREAST IMPLANT	11/21/2012	4/23/2019	7 yrs.	
9617229-2022-02816	TEXTURED EXPANDER	TISSUE EXPANDER	7/23/2007	11/15/2007	4 mos	6/11/2019
		BREAST IMPLANT	11/15/2007	7/1/2019	12 yrs.	
9617229-2022-02773	TEXTURED EXPANDER	TISSUE EXPANDER	2/10/2015	9/8/2015	7 mos	8/2019
		BREAST IMPLANT	9/8/2015	9/15/2019	4 yrs.	
9617229-2022-00158	TEXTURED EXPANDER	TISSUE EXPANDER	6/3/2013	9/12/2013	3 mos	7/15/2021
		BREAST IMPLANT	9/12/2013	10/1/2021	8 yrs.	
9617229-2017-00119	UNKNOWN	TISSUE EXPANDER	Not provided	Not provided	8 mos	Not provided
		SMOOTH BREAST IMPLANTS	Not provided	Not provided	6 yrs	
9617229-2020-22724	TEXTURED EXPANDER	TISSUE EXPANDER	Not provided	Not provided	Not provided	Not provided
1645337-2012-00165	UNKNOWN	BREAST IMPLANTS	11/15/2010	6/28/2012	2 yrs	Not provided

Figure 2 below shows the number of tissue expanders MDRs received for each year since 1993 through April 1, 2022. A significant increase in the number of reports received is noted for 2018-2021. This spike may be attributed to the 2018 panel meeting and a 2019 recall on Allergan textured tissue expanders.

Figure 2: Number of MDRs received for tissue expanders since 1993



There were 5,573 serious injury MDRs for the product code LCJ that were received through the Alternate Summary Reporting (ASR) Program. The top patient problem codes of the ASR MDRs are summarized in Table 16 below.

Table 16: Top Patient Problem Codes submitted through ASR

Patient Problem	Total Number
Systemic Symptoms	5
Extrusion	33
Deflation	78
Pain	42
Seroma	53
Infection	350
Capsular Contracture	304
Surgical procedure	759
Implant failure	769
Unknown/Blank	2,358

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