OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE
Breast

Implant-based Breast Reconstruction after Mastectomy for Breast Cancer: A Systematic Review and Meta-analysis

Ian J. Saldanha, MBBS, MPH, PhD*†
Justin M. Broyles, MD‡
Gaelen P. Adam, MLIS, MPH*
Wangnan Cao, PhD*
Monika Reddy Bhuma, BDS, MPH*
Shivani Mehta, MPH*
Andrea L. Pusic, MD, MS‡
Laura S. Dominici, MD§
Ethan M. Balk, MD, MPH*

Background: Women undergoing implant-based reconstruction (IBR) after mastectomy for breast cancer have numerous options, including timing of IBR relative to radiation and chemotherapy, implant materials, anatomic planes, and use of human acellular dermal matrices. We conducted a systematic review to evaluate these options.
Methods: We searched Medline, Embase, Cochrane CENTRAL, CINAHL, and ClinicalTrials.gov for studies, from inception to March 23, 2021, without language restriction. We assessed risk of bias and strength of evidence (SoE) using standard methods.
Results: We screened 15,936 citations. Thirty-six mostly high or moderate risk of bias studies (48,419 patients) met criteria. Timing of IBR before or after radiation may result in comparable physical, psychosocial, and sexual well-being, and satisfaction with breasts (all low SoE), and probably comparable risks of implant failure/loss or explantation (moderate SoE). No studies addressed timing relative to chemotherapy. Silicone and saline implants may result in clinically comparable satisfaction with breasts (low SoE). Whether the implant is in the prepectoral or total submuscular plane may not impact risk of infections (low SoE). Acellular dermal matrix use probably increases the risk of implant failure/loss or need for explant surgery (moderate SoE) and may increase the risk of infections (low SoE). Risks of seroma and unplanned repeat surgeries for revision are probably comparable (moderate SoE), and risk of necrosis may be comparable with or without human acellular dermal matrices (low SoE).
Conclusions: Evidence regarding IBR options is mostly of low SoE. New high-quality research is needed, especially for timing, implant materials, and anatomic planes of implant placement. *(Plast Reconstr Surg Glob Open 2022;10:e4179; doi: 10.1097/GOX.0000000000004179; Published online 18 March 2022.)*

INTRODUCTION

More than 40% of US women who undergo mastectomy for breast cancer have breast reconstruction,[1] amounting to about 107,000 women in 2019.[2] Most reconstruction procedures in the United States (81%) are implant-based.[2] Considerations for implant-based reconstruction (IBR) include procedure timing relative to chemotherapy and radiation, implant material (eg, silicone, saline, double-lumen), anatomic plane (prepectoral, partial submuscular, or total submuscular), and use of an adjunctive human acellular dermal matrix (ADM). Each consideration can impact aesthetics, complications, and cost.

Objectives

We conducted a systematic review (SR) for the Agency for Healthcare Research and Quality (AHRQ) to support the American Society of Plastic Surgeons in development of a new clinical practice guideline on breast reconstruction after mastectomy.[3] Here, we focus on the research

*From the *Center for Evidence Synthesis in Health, Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, R.I.; †Department of Epidemiology, Brown University School of Public Health, Providence, R.I.; ‡Division of Plastic and Reconstructive Surgery, Department of Plastic Surgery, Harvard Medical School, Boston, Mass.; and §Division of Breast Surgery, Department of Surgery, Harvard Medical School, Boston, Mass.*

Received for publication November 23, 2021; accepted January 13, 2022.

DOI: 10.1097/GOX.0000000000004179

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. This study was funded under Contract No. HHSA 75Q80120D00001 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services (DHHS).*

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

questions concerning IBR. Other articles in this issue focus on autologous reconstruction[4] and the comparison between IBR and autologous reconstruction.[5] All reports focus on women who are undergoing (or who have undergone) mastectomy for breast cancer treatment or prophylaxis. Here, we evaluate the comparative benefits and harms of (1) timing relative to chemotherapy and radiation, (2) implant materials, (3) implant placement planes, and (4) use of human ADMs. We evaluate whether outcomes varied by age, breast cancer stage, occurrence (first/recurrent), chemotherapy/radiation type, timing (immediate/delayed), number of stages (single/multiple), laterality (unilateral/bilateral), implant surface (smooth/textured), implant shape (round/teardrop), and implant size.

METHODS

We used standard SR methodology as outlined in AHRQ's Methods Guide.[6] We refined the research questions and protocol after discussions with groups of experts. We registered the SR protocol through PROSPERO (CRD42020193183).

Search Strategy

We searched for published studies in Medline (via PubMed), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL, and for unpublished studies in ClinicalTrials.gov. The searches (for the full SR) included terms related to breast cancer, mastectomy, implants, ADM, and autologous reconstruction. (**See table 1, Supplemental Digital Content 1,** which displays the search strategies. **http://links.lww.com/PRSGO/B950**.)

No date or language restrictions were applied. All searches are current as of March 23, 2021. We also scanned the reference lists of available SRs for potentially eligible studies.

Study Selection

Seven investigators independently screened each title and abstract using Abstrackr (http://abstrackr.cebm.brown.edu/). All accepted citations were rescreened in duplicate in full text. At both stages, discrepancies were resolved through discussion and/or consultation with a third investigator.

We included studies of adult women (aged ≥18 years) who had undergone mastectomy for breast cancer or carcinoma in situ (or for cancer prophylaxis) and had IBR. Here, we focus on outcomes prioritized by stakeholder panels. (**See table 2, Supplemental Digital Content 2,** which displays the outcomes of interest for each research question. **http://links.lww.com/PRSGO/B951**.)

Additional outcomes are reported in the full report.[3] For benefit outcomes, we included randomized controlled trials (RCTs) with 10 or more patients per group and prospective/retrospective nonrandomized comparative studies (NRCSs) with adequate statistical adjustment analyses and 30 or more patients per group. For surgical complications, we also included single-group studies with 500 patients or more.

Takeaways

Question: What are the comparative benefits and harms of various timing, materials, anatomic planes, and human acellular dermal matrix (ADM) use options for implant-based reconstruction (IBR)?

Findings: In a large systematic review and meta-analysis, 36 studies met criteria. Timing IBR before/after radiation results in comparable physical/psychosocial/sexual well-being, satisfaction with breasts, and risk of implant failure/loss (no studies addressed timing relative to chemotherapy). Silicone/saline implants have comparable satisfaction with breasts. Prepectoral/total submuscular implants have similar risks of infections. ADMs increase risk of implant failure/loss and infections, but risks of seroma, unplanned repeat surgeries, and necrosis are comparable.

Meaning: Evidence regarding IBR options is of low strength.

Risk of Bias Assessment and Data Extraction

For each study, one investigator assessed risk of bias and extracted data into the Systematic Review Data Repository Plus (http://srdrplus.ahrq.gov/). All extractions were verified by a second investigator. We used questions from the Cochrane Risk of Bias,[7] Risk of Bias in Nonrandomized Studies of Interventions,[8] and National Heart, Lung, and Blood Institute Quality Assessment[2] tools.

Syntheses

For dichotomous outcomes, we preferentially evaluated odds ratios (ORs). For continuous outcomes, we evaluated net mean differences (NMDs) (difference-in-differences) for outcomes measured at both baseline and postintervention, or mean differences (MDs) for outcomes measured only postintervention. When appropriate, we estimated these based on reported data. When feasible, for continuous outcomes, we made conclusions based on published estimates of minimal clinically important differences (MCIDs). For NRCSs, we considered only reported adjusted analyses. Where there were three or more studies reporting results from similar analyses, we conducted pairwise meta-analyses using random-effects models in Stata.

Strength of Evidence (SoE) Assessment

We graded SoE as per the AHRQ Methods Guide.[6] We considered risk of bias, consistency, precision, directness, and sparsity. For each prioritized outcome, we assigned a SoE rating of high, moderate, low, or insufficient. Grades of high, moderate, and low indicate the degree of confidence we have that the estimate lies close to the true effect; an insufficient rating indicates that the evidence precluded estimation of an effect.[6] In accordance with AHRQ guidance,[9,10] we use qualifying language regarding SoE when communicating conclusions: "probably" for moderate SoE and "may" for low SoE.

RESULTS

For the full SR, our searches yielded 15,936 citations (Fig. 1). We screened 1352 full-text articles, of which 36 were eligible for the research questions described in this article.

Characteristics of Included Evidence

Published between 2005 and 2021, the 36 included studies comprised three RCTs[11–13] and 33 NRCSs, with adequate statistical adjustment analyses,[14–56] with a total of 48,419 women (Table 1). Twenty-three studies (64%) were from the United States, four (11%) from South Korea, three (8%) from Canada, and three (8%) from the United States and Canada. One study each (3%) was from Italy, Sweden, and Turkey.

Most studies (72%–94%) did not report participant age, race, or body mass index (BMI) for the entire study population. Where reported for the entire population, average patient ages ranged from 46.2 to 51.2 years (12 studies) and average BMIs from 22.3 to 27.0 kg/m^2 (nine studies). In two studies,[27,30,57] 79% and 94% of patients were White, and 6.4% and 1.3% were Black. In the one study with data,[28] all patients were treated for their first occurrence of breast cancer. In the two studies with data on reasons for mastectomy, one reported that 90% of mastectomies were therapeutic and 10% prophylactic,[25,51] whereas the other reported that 44% were therapeutic and 56% prophylactic.[43]

Risk of Bias

Two of the three RCTs had a moderate risk of bias and one had a high risk. (**See table 3, Supplemental Digital Content 3,** which displays the risk of bias assessments. **http://links.lww.com/PRSGO/B952**.)

The primary concerns about bias in the RCTs were lack of blinding of participants and care providers, evidence of selective outcome reporting, and incompleteness of outcome data. Among the 33 NRCSs, 26 had a high risk of bias, six moderate risk, and one low risk. The primary concerns about bias in the NRCSs were evidence of serious risk of confounding and lack of blinding of outcome assessors.

Timing Relative to Chemotherapy and Radiation

No eligible studies evaluated timing relative to of chemotherapy. Five NRCSs, reported in 10 articles,[21,23,26,44,45,47–49,52,56] and no RCTs evaluated timing relative to radiation in 2834 patients (between 130 and 1143 patients each) (Table 1). Four NRCSs were at a high and one at a moderate risk of bias. Table 2 summarizes the evidence for all comparisons in the review.

Benefit Outcomes: Two NRCSs (Yoon et al[56] and Cordeiro et al[21]) compared IBR before versus after radiation and reported comparable well-being and satisfaction using subscales of the BREAST-Q (each scored 0–100; higher scores indicate better outcomes). (**See table 4, Supplemental Digital Content 4**, which displays summary tables. **http://links.lww.com/PRSGO/B953**.)

Yoon et al[56] reported an adjusted MD (adjMD) of −0.64 [95% confidence interval (CI) −7.19 to 5.90) for physical well-being (MCID = 3[58]), 0.48 (95% CI −7.72 to 8.68) for psychosocial well-being (MCID = 4[58]), −1.00 (95% CI −8.41 to 6.40) for sexual well-being (MCID = 5[58]), and −3.89

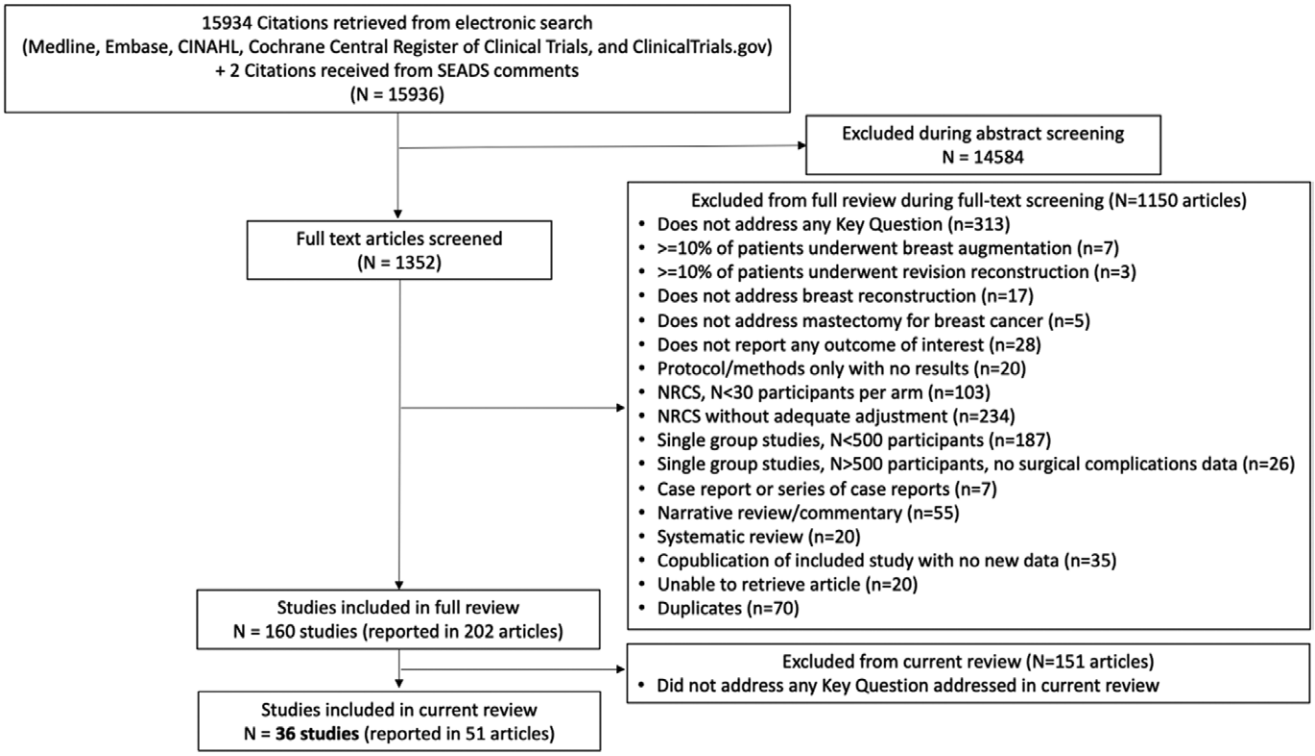

Fig. 1. PRISMA diagram depicting identification of studies in this SR.

Table 1. Summary of Design, Arm, and Sample Details

Study, Publication Year, PMID, Country	Design (Funding) (Study Years)	Risk of Bias	Eligibility Criteria	Arm	Implant Details (%) (Only Reported Details)	Reconstruction Details (%) (Only Reported Details)	N	Age (y), Mean (SD) or As Specified	Race (%)	Breast Cancer Occurrence %	Cancer Stage or Mastectomy Purpose (%)
TIMING OF CHEMOTHERAPY AND RADIATION RELATIVE TO IBR											
Cordeiro et al,[21] 25742523, USA	NRCS (Industry) (2003–2012)	High	I: IBRE: combined AR plus TE/ implant BR, peri-operative radiation, delayed BR	IBR before radiation	NR	Laterality: uni (71.6)/bi (28.4) Stages: >1 (100)	NR	46.3 (8.9)	NR	NR	NR
				IBR after radiation	NR	Laterality: uni (57)/bi (43) Stages: >1 (100)	NR	46.1 (10.6)	NR	NR	NR
				Total	N/A	N/A	1143	NR	NR	NR	NR
Eriksson et al,[23] 24258257, Sweden	NRCS (NR) (2007–2011)	High	I: immediate IBRE: only risk-reducing surgery	IBR before radiation	PLANE: partial submuscular (100)	Timing: imm (100) Chemo: after (57.57)/ no chemotherapy (42.11)	304	Median 46; range 21, 74	NR	NR	Stage 0 (9.54), stage NR (90.46)
				IBR after radiation	PLANE: partial submuscular (100)	Timing: imm (100) Chemo: after (32.25)/ no chemotherapy (65.63)	64	Median 55; range 28, 75	NR	NR	Stage 0 (28.13), stage NR (70.31)
				Total	N/A	N/A	368	NR	NR	NR	NR
Hirsch et al,[26] 25347643, USA	NRCS (NR) (1998–2008)	High	I: immediate TE/IBR	IBR before radiation	NR	Timing: imm (100)Stages: >1 (100)	NR	NR	NR	NR	NR
				IBR after radiation	NR	Timing: imm (100)Stages: >1 (100)	NR	NR	NR	NR	NR
				Total	N/A	N/A	876	Mean 48.1; range 16.1, 57.6	NR	NR	NR
Stein et al,[52] 32561384, Canada	NRCS (none) (2010–2019)	High	I: immediate IBR with radiation	IBR before radiation	Size: mean 406 cm^3	Laterality: NRTiming: imm (100)Stages: 1 (53.9)/>1 (46.1) Chemo: before (100) Radiation: before (100)	76	47.2 (NR)	NR	NR	NR
				IBR after radiation	Size: mean 444 cm^3	Laterality: NRTiming: imm (100)Stages: 1 (50)/>1 (50)Chemo: after (100) Radiation: after (100)	54	54.7 (NR)	NR	NR	NR
				Total	N/A	N/A	130	50.3 (NR)	NR	NR	NR
Yoon et al,[56] 32332528, USA & Canada	NRCS (nonindustry) (2012–2015)	Moder-ate	I: Immediate TE/ IBR with PMRT	IBR before radiation	NR	Laterality: uni (38.8)/ bi (61.2)Timing: imm (100)Stages: >1 (100) Chemo: before (92.5)/ after (7.5)Radiation: after (100)	80	45.3 (10.1)	W (93.6), others (6.4)	NR	NR
				IBR after radiation	NR	Laterality: uni (42.6)/ bi (57.4)Timing: imm (100)Stages: >1 (100) Chemo: before (60.8)/ after (39.2)Radiation: before (100)	237	47.4 (10.4)	W (87.6), others (12.4)	NR	NR
				Total	N/A	N/A	317	NR	NR	NR	NR

(*Continued*)

Table 1. (*Continued*)

Study, Publication Year, PMID, Country	Design (Funding) (Study Years)	Risk of Bias	Eligibility Criteria	Arm	Implant Details (%) (Only Reported Details)	Reconstruction Details (%) (Only Reported Details)	N	Age (y), Mean (SD) or As Specified	Race (%)	Breast Cancer Occurrence %	Cancer Stage or Mastectomy Purpose (%)
COMPARISON OF MATERIALS FOR IBR											
Antony et al,[14] 24135689, USA	NRCS (none) (1997–2007)	High	I: two-staged bilateral IBR	IBR with silicone	NR	Laterality: bi (100) Stages: >1 (100)	NR	NR	NR	NR	Stage NR (100)
				IBR with saline	NR	Laterality: bi (100) Stages: >1 (100)	NR	NR	NR	NR	Stage NR (100)
				Total	N/A	N/A	365	47 (9.4)	NR	NR	Stage NR (100)
Cordeiro et al,[21] 25742523, USA	NRCS (industry) (2003–2012)	High	I: IBRE: combined AR plus TE/ implant BR, peri-operative radiation, delayed BR	IBR with silicone	NR	Stages: >1 (100)	NR	NR	NR	NR	NR
				IBR with saline	NR	Stages: >1 (100)	NR	NR	NR	NR	NR
				Total	N/A	N/A	1143	NR	NR	NR	NR
Le et al,[30] 15743498, USA	NRCS (non-industry) (1993–1994)	High	I: age <65 y; early-stage/unstaged first primary breast cancer treated with mastectomyE: missing implant information; bilateral implants of discordant types	IBR with silicone	NR	NR	333	NR	NR	NR	NR
				IBR with saline	NR	NR	149	NR	NR	NR	NR
				IBR with double-lumen implants	NR	NR	314	NR	NR	NR	NR
				Total	N/A	N/A	796	NR	W (94.2), B (1.3), A (1.6), H (2)	NR	NR
Macadam et al,[35] 20009795, Canada	NRCS (nonindustry) (NR)	High	I: IBR	IBR with silicone	NR	Laterality: uni (40)/ bi (60)Timing: imm (82.67)/del (17.33) Chemo: timing NR (60)/No chemotherapy (40)Radio: timing NR (37.33)/none(62.67)	75	52.27 (9.54); <45 years (25.33%), ≥45 years (74.67%)	W (34.78), A (57.97), others (7.25)	NR	None (5.33), stage 0 (42.67), stage NR (52)
				IBR with saline	Surface: smooth (100)Shape: round (100)	Laterality: uni (44.12)/ bi (55.88)Timing: imm (61.76)/del (35.29)/ mixed (2.94) Chemo: timing NR (47.06)/no chemotherapy (52.94) Radio: timing NR (38.24)/none(71.76)	68	55.62 (9.14); <45 y (14.49%), ≥45 y (85.51%)	W (23.64), A (74.6), others (4.76)	NR	None (4.48), stage 0 (35.82), stage NR (59.7)
				Total	N/A	N/A	143	NR	NR	NR	NR
McCarthy et al,[36] 21136577, USA & Canada	NRCS (NR) (2006–2007)	High	I: Age ≥21 y; IBR	IBR with silicone	NR	Laterality: uni (47.2)/ bi (52.8)Timing: imm (65.9)/del (34.1) Radio: before (25)/ after (23.3)	176	53.7 (11)	W (92), B (1.1), A (1.7), others (5.2)	NR	NR
				IBR with saline	NR	Laterality: uni (60.1)/ bi (39.9)Timing: imm (74.2)/del (25.8) Radio: before (20.3)/after (19.3)	306	51.3 (10.4)	W (87.8), B (4), A (4), others (4.2)	NR	NR
				Total	N/A	N/A	482	NR	NR	NR	NR

(*Continued*)

Table 1. (*Continued*)

Study, Publication Year, PMID, Country	Design (Funding) (Study Years)	Risk of Bias	Eligibility Criteria	Arm	Implant Details (%) (Only Reported Details)	Reconstruction Details (%) (Only Reported Details)	N	Age (y), Mean (SD) or As Specified	Race (%)	Breast Cancer Occurrence %	Cancer Stage or Mastectomy Purpose (%)
COMPARISON OF ANATOMIC PLANES FOR IBR											
Lee et al,[11] 33691448, South Korea	RCT (None) (2018–2019)	Moderate	I: age 30–60; immediate IBR E: advanced-stage III or IV breast cancer	Prepectoral	Material: silicone (100) Surface: textured (100) ADM: yes (100)	Laterality: uni (100) Timing: imm (100) Chemo: timing NR (30) Radio: timing NR (25)	20	46.2 (7.1)	NR	NR	Stage 0: 30 Stage I: 30 Stage II: 40
				Partial submuscular	Material: Silicone (100) Surface: textured (100) ADM: yes (100)	Laterality: uni (100) Timing: imm (100) Chemo: timing NR (42.9) Radio: timing NR (35.7)	14	46.8 (4.4)	NR	NR	Stage 0: 21.4 Stage I: 42.9 Stage II: 35.7
				Total	N/A	N/A	34	NR	NR	NR	NR
Avila et al, 2020,[15] 33234947, USA	NRCS (none) (2014–2018)	High	I: IBR	Prepectoral	NR	Laterality: uni (14.8)/bi (85.2) Timing: imm (97)/del (3) Stages: 1 (73.9)/ 2 (26.1) Chemo: before (15.3) Radio: timing NR (3.5)	203	46.5 (10.0)	NR	NR	NR
				Total submuscular	NR	Laterality: uni (12.9)/Bi (87.1) Timing: imm (97)/del (3) Stages: 1 (33.2)/ 2 (66.8) Chemo: before (14.4) Radio: timing NR (0.5)	202	45.9 (10.4)	NR	NR	NR
				Total	N/A	N/A	405	46.2 (10.2)	NR	NR	NR
Cattelani et al, [18] 29275104, Italy	NRCS (NR) (2015–2016)	High	I: Age <75 y, no previous radiation, BMI <30 kg/m^{2}E: T4 or M+ breast tumors	Prepectoral	Material: silicone (100)Surface: textured (100)Shape: anatomic/ teardrop (100) Size: mean 390.9 ml, range 180, 570	Laterality: uni (82.05)/ bi (17.95)Timing: imm (100)Stages: 1 (100) Chemo: before (10.26)/ after (28.21)/no chemotherapy (61.53) Radio: timing NR (13.04)/none (86.96)	39	52.9 (NR); range 36, 71	NR	NR	NR
				Total submuscular	Surface: textured (100)Size: mean 361.5 ml, range 190, 650	Laterality: uni (82.22)/ bi (17.78)Timing: imm (100)Stages: 1 (73.3)/>1 (26.7) Chemo: before (8.89)/ after (37.78)/no chemotherapy (53.33) Radio: timing NR (20.76)/none(79.24)	45	52.3 (NR); range 26, 75	NR	NR	NR
				Total	N/A	N/A	84	NR	NR	NR	NR

(*Continued*)

Table 1. (*Continued*)

Study, Publication Year, PMID, Country	Design (Funding) (Study Years)	Risk of Bias	Eligibility Criteria	Arm	Implant Details (%) (Only Reported Details)	Reconstruction Details (%) (Only Reported Details)	N	Age (y), Mean (SD) or As Specified	Race (%)	Breast Cancer Occurrence %	Cancer Stage or Mastectomy Purpose (%)
Gabriel et al,[24] 32195862, USA	NRCS (none) (2009–2017)	High	I: immediate two-stage IBR; BMI ≥30 E: revision reconstruction	Prepectoral	NR	Laterality: uni (52.7)/ bi (47.3)Timing: imm (100) Chemo: before (13.2)/ after (5.9) Radio: before (3.9)/after (1.6)	68	Median: 49 (IQR 33, 76)	NR	NR	NR
				Partial submuscular	NR	Laterality: uni (50.8)/bi (49.2)Chemo: before (12.3)/after (30.8) Radio: before (3.1)/ after (10.9)	65	Median: 53 (IQR 28, 73)	NR	NR	NR
				Total	N/A	N/A	133	NR	NR	NR	NR
Kim and Hong,[28] 33066236, South Korea	NRCS (none) 2015–2020)	Moderate	I: immediate unilateral single-stage IBR with ADM E: previous breast surgery or radiation	Prepectoral	Size: mean 249.0 cm^3 (SD 104.8) ADM: yes (100)	Laterality: uni (100) Timing: imm (100) Stages: 1 (100) Chemo: before (5.7)/after (32.1) Radio: timing NR (11.3)	53	47.7 (7.5)	NR	1st: 100	Stage I: 73.6 Stage II: 20.8 Stage III: 5.7
				Partial submuscular	Size: mean 268.1 cm^3 (SD 103.0) ADM: yes (100)	Laterality: uni (100) Timing: imm (100) Stages: 1 (100) Chemo: before (10.5)/ after (43.0) Radio: timing NR (18.4)	114	46.6 (8.7)	NR	1st: 100	Stage I: 66.7 Stage II: 21.0 Stage III: 10.2
				Total	N/A	N/A	167	NR	NR	1st: 100	NR
Kraenzlin et al,[29] 32568752, USA	NRCS (none) 2016–2018)	High	I: adults; IBR with TE	Prepectoral	NR	Laterality: uni (40.8)/ bi (59.2)Timing: del (100)Stages: >1 (100) Chemo: before (21.9)/ after (13.6)Radio: before (11.8)/after (7.1)	169	48.8	NR	NR	NR
				Total submuscular	NR	Laterality: uni (47.0)/ bi (53.0)Timing: del (100)Stages: >1 (100) Chemo: before (26.5)/ after (17.1)Radio: before (28.2)/after (10.3)	117	49.4	NR	NR	NR
				Total	N/A	N/A	286	NR	NR	NR	NR

(*Continued*)

Table 1. (*Continued*)

Study, Publication Year, PMID, Country	Design (Funding) (Study Years)	Risk of Bias	Eligibility Criteria	Arm	Implant Details (%) (Only Reported Details)	Reconstruction Details (%) (Only Reported Details)	N	Age (y), Mean (SD) or As Specified	Race (%)	Breast Cancer Occurrence %	Cancer Stage or Mastectomy Purpose (%)
Nealon et al,[37] 32032345, USA	NRCS (none) (2014–2018)	High	I: Direct-to-implant BR	Prepectoral	Surface: smooth (100)Shape: round (100) Size: mean 468.2 ml, SD 174.7	Laterality: uni (39.5)/ bi (60.5)Timing: imm (100)Stages: 1 (100) Chemo: timing NR (38.6)/no chemotherapy (61.4)Radio: timing NR (36.8)/none (63.2)	114	52.7 (12.4); median 51.5; IQR 47.8, 62	NR	NR	Stage I (43.9), Stage II (17.5), Stage III (6.1)
				Total submuscular	Surface: smooth (100)Shape: round (100) Size: mean 417.2 ml, SD 141.8	Laterality: uni (32.4)/ bi (67.6)Timing: imm (100)Stages: 1 (100) Chemo: timing NR (31.7)/no chemotherapy (68.3)Radio: timing NR (36.7)/none (63.3)	142	50.7 (10.4); median 51; IQR 43.8, 58	NR	NR	Stage I (44.4), Stage II (18.3), Stage III (7), Stage IV (1.4)
				Total	N/A	N/A	256	NR	NR	NR	NR
Ozgur, [39] 33223365, Turkey	NRCS (NR) (2012–2015)	High	I: Immediate single-staged IBR after therapeutic mastectomy	Partial submuscular	Size: mean 375.7 mm^3 (SD 75.7)	Laterality: uni (82.4)/bi (17.6) Timing: imm (100) Stages: 1 (100)Chemo: before (33.0) Radio: before (3.3)/after (56.0)	83	43.7 (10.2)	NR	1st: 96.7 Recurrent: 3.3	Therapeutic: 100
				Total submuscular	Size: mean 373 mm^3 (SD 80.9)	Laterality: uni (82.9)/bi (17.1) Timing: imm (100) Stages: 1 (100) Chemo: before (32.5) Radio: before (9.4)/after (55.6)	107	43.0 (9.4)	NR	1st: 90.6 Recurrent: 9.4	Therapeutic: 100
				Total	N/A	N/A	190	NR	NR	NR	Therapeutic: 100
USE VERSUS NONUSE OF HUMAN ADMS DURING IBR											
McCarthy et al,[12] 23096987, NCT006 39106, USA	RCT (nonindustry) (NR)	Moderate	I: Age ≥21 y; immediate TE/ IBRE: Single-stage IBR and/ or combined AR + TE/IBR; prior irradiation to the ipsilateral breast/ chest; history of prior axillary lymph node dissection	IBR with human ADM	Plane: total submuscular (100)	Laterality: uni (48)/bi (52)Timing: imm (100) Stages: >1 (100)Chemo: before (6)/after (30)/ no chemotherapy (64)	36	IQR 29, 69	NR	NR	NR
				IBR without human ADM	NR	Laterality: uni (44)/bi (56)Timing: imm (100) Stages: >1 (100)Chemo: before (6)/after (25)/ no chemotherapy (69)	33	IQR 32, 72	NR	NR	NR
				Total	N/A	N/A	69	NR	NR	NR	NR

(*Continued*)

Table 1. (*Continued*)

Study, Publication Year, PMID, Country	Design (Funding) (Study Years)	Risk of Bias	Eligibility Criteria	Arm	Implant Details (%) (Only Reported Details)	Reconstruction Details (%) (Only Reported Details)	N	Age (y), Mean (SD) or As Specified	Race (%)	Breast Cancer Occurrence %	Cancer Stage or Mastectomy Purpose (%)
Wendel,[13] none, USA	RCT (nonindustry) (2007–2011)	High	I: TE/IBR	IBR with human ADM	NR	NR	20	NR	NR	NR	NR
				IBR without human ADM	NR	NR	16	NR	NR	NR	NR
				Total	N/A	N/A	36	18–65 years (83.3%), ≥65 y (16.7%)	NR	NR	NR
Brooke et al,[17] 22868313, USA	NRCS (none) (2000–2010)	High	I: TE/IBRE: prior major breast surgery or BR	IBR with use of human ADM	NR	Laterality: uni (31.3)/bi (68.7) Stages: >1 (100)	131	50 (12.1)	NR	NR	Stage NR (100)
				IBR without use of human ADM	NR	Laterality: uni (47.6)/bi (52.4) Stages: >1 (100) Chemo: timing NR (38)	42	46 (10.7)	NR	NR	Stage NR (100)
				Total	N/A	N/A	173	49.7 (10.7)	NR	NR	Stage NR (100)
Cattelani et al,[18] 29275104, Italy	NRCS (NR) (2015–2016)	High	I: age < 75 years, no previous radiotherapy, BMI <30 kg/m²E: T4 or Mþ breast tumors, previous surgery of the same breast	IBR with prepectoral placement	Material: silicone (100)Surface: textured (100) Shape: anatomic/teardrop (100)Size: mean 390.9 ml, range 180, 570 Plane: prepectoral (100)	Laterality: uni (82.05)/bi (17.95)Timing: imm (100)Stages: 1 (100)Chemo: before (10.26)/after (28.21)/no chemotherapy (61.53) Radio: timing NR (13.04)/none (86.96)	39	52.9 (NR); range 36, 71	NR	NR	NR
				IBR with total submuscular placement	Surface: textured (100) Size: mean 361.5 ml, range 190, 650Plane: total submuscular (100)	Laterality: uni (82.22)/bi (17.78)Timing: imm (100)Stages: 1 (73.3)/>1 (26.7)Chemo: before (8.89)/after (37.78)/no chemotherapy (53.33) Radio: timing NR (20.76)/none (79.24)	45	52.3 (NR); range 26, 75	NR	NR	NR
				Total	N/A	N/A	84	NR	NR	NR	NR
Chun et al,[19] 20124828, USA	NRCS (NR) (2002–2008)	High	I: immediate TE/implant or AR + TE/implantE: delayed AR	IBR with use of human ADM	NR	Timing: imm (100)Chemo: before (14.9)/after (19)/no chemotherapy (66.1) Radio: before (8.7)/after (6.5)/none(85.9)	269 breasts	47 (10.5)	NR	NR	Stage 0 (71.4), Stage I (4.1), stage II (12.3), stage III (12.3)
				IBR without use of human ADM	NR	Timing: imm (100) Chemo: before (8.2)/after (30.8)/no chemotherapy (61)Radio: before (5.2)/after (8.6)/none (86.2)	146 breasts	46.2 (8.4)	NR	NR	Stage 0 (66.4), stage I (8.2), stage II (13.7), stage III (11.6)
				Total	N/A	N/A	283	NR	NR	NR	NR

(*Continued*)

Table 1. (*Continued*)

Study, Publication Year, PMID, Country	Design (Funding) (Study Years)	Risk of Bias	Eligibility Criteria	Arm	Implant Details (%) (Only Reported Details)	Reconstruction Details (%) (Only Reported Details)	N	Age (y), Mean (SD) or As Specified	Race (%)	Breast Cancer Occurrence %	Cancer Stage or Mastectomy Purpose (%)
Craig et al,[22] 29800083, USA	NRCS (none) (2004–2014)	Low	I: TE/implant BRE: premastectomyradiation	IBR with human ADM	NR	Timing: imm (100)Stages: >1 (100)Radio: after (15.3)	NR	49 (10.6); range 29, 68	NR	NR	Ther (100)
				IBR without human ADM	NR	Timing: imm (100)Stages: >1 (100)Radio: after (14.2)	NR	48.4 (10.6); range 28, 72	NR	NR	Ther (100)
				Total	N/A	N/A	957	NR	NR	NR	NR
Ganesh Kumar et al[25] 33172826, USA & Canada	NRCS (non-industry) (2012–2015)	Moderate	I: TE/IBR	IBR with human ADM	NR	Laterality: uni (38.9)/Bi (61.1)Timing: imm (100)Stages: >1 (100)Chemo: before (69.8)/after (30.2)Radiation: before (3.7)/after (21.3)	738	48.7 (10.5)	NR	NR	Ther (85.8), proph (14.2)
				IBR without human ADM	NR	Laterality: uni (38.8)/Bi (61.2)Timing: imm (100)Stages: >1 (100)Chemo: before (61.9)/after (38.1)Radiation: before (5.9)/after (20.9)	713	48.1 (10.1)	NR	NR	Ther (93.3), proph (6.7)
				Total	N/A	N/A	1451	48.4 (10.3)	NR	NR	Ther (89.5), proph (10.5)
Hirsch et al,[26] 25347643, USA	NRCS (NR) (1998–2008)	Low	L: immediate TE/IBR	IBR with human ADM	NR	Timing: imm (100)Stages: >1 (100)	201	NR	NR	NR	NR
				IBR without human ADM	NR	Timing: imm (100)Stages: >1 (100)	675	NR	NR	NR	NR
				Total	N/A	N/A	876	Mean 48.1; range 16.1, 57.6	NR	NR	NR
Ibrahim,[27] 24165587, USA	NRCS (none) (2005–2011)	Moderate	I: immediate or delayed TE/IBRE: AR with or without ADM	IBR with human ADM	NR	NR	3283	50.7 (10.6)	W (83), B (5.7), A (2.9), H (0.3), other 1 (0.1), other 2 (0.2), other 3 (7.9)	NR	NR
				IBR without human ADM	NR	NR	15714	51.3 (10.8)	W (78.7), B (6.6), A (28), H (0.8), other 1 (0.1), other 2 (0.2), other 3 (11)	NR	NR
				Total	N/A	N/A	18977	51.2 (10.7)	W (79.4), B (6.4), A (2.8), H (0.1), other 1 (0.1), other 2 (0.2), other 3 (10.3)	NR	NR

(*Continued*)

Table 1. (*Continued*)

Study, Publication Year, PMID, Country	Design (Funding) (Study Years)	Risk of Bias	Eligibility Criteria	Arm	Implant Details (%) (Only Reported Details)	Reconstruction Details (%) (Only Reported Details)	N	Age (y), Mean (SD) or As Specified	Race (%)	Breast Cancer Occurrence %	Cancer Stage or Mastectomy Purpose (%)
Lee et al,[32] No PMID, South Korea	NRCS (NR) (2773838010-2016938)	High	I: immediate unilateral TE/IBR	IBR with human ADM	NR	Laterality: uni (100) Timing: imm (100) Stages: >1 (100)	738	NR	NR	NR	NR
				IBR without human ADM	NR	Laterality: uni (100) Timing: imm (100) Stages: >1 (100)	693	NR	NR	NR	NR
				Total	N/A	N/A	1431	43.8 (7.5)	NR	NR	NR
Liu et al,[34] 21228744, USA	NRCS (NR) (2004–2011)	High	I: immediate IBRE: delayed reconstruction; AR	IBR with human ADM	NR	Timing: imm (100)Radio: NR (9.8)/none (90.2)	266	NR	NR	NR	NR
				IBR without human ADM	NR	Timing: imm (100)Radio: timing NR (10.4)/none (89.6)	242	NR	NR	NR	NR
				Total	N/A	N/A	508	NR	NR	NR	NR
Nealon et al,[38] 31605310, USA	NRCS (none) (2008–2018)	High	I: unilateral breast cancer, bilateral mastectomy, and immediate IBRE: bilateral AR; delayed contralateral prophylactic mastectomy and BR	IBR with human ADM	NR	Timing: imm (100)	1488 breasts	NR	NR	NR	NR
				IBR without human ADM	NR	Timing: imm (100)	668 breasts	NR	NR	NR	NR
				Total	N/A	N/A	1117	NR	NR	NR	NR
Pannucci et al,[40] 23508050, USA	NRCS (non-industry) (2008–2011)	Moderate	I: TE/IBRE: mastopexy/breast augmentation	IBR with human ADM	NR	NR	3450	NR	NR	NR	NR
				IBR without human ADM	NR	NR	10799	NR	NR	NR	NR
				Total	N/A	N/A	14249	<40 y (15%), 40–60 y (57.5%), ≥60 y (21.1%)	NR	NR	NR
Peled et al,[41] 2012, 22634688, USA	NRCS (NR) (2006–2010)	High	I: immediate TE/IBR	IBR with human ADM	Surface: textured (100) Plane: total submuscular (100)	Timing: imm (100)Stages: >1 (100)Chemo: before (36)/after (21)/no chemotherapy (43)Radio: before (9)/after (14)/none (77)	65	48.2 (NR)	NR	NR	Ther (55), proph (45)
				IBR without human ADM	Plane: total submuscular (100)	Timing: imm (100)Stages: >1 (100)Chemo: before (44.4)/after (23.3)/no chemotherapy (32.3) Radio: before (4.4)/after (23.3)/none (72.3)	63	44.6 (NR)	NR	NR	Ther (66.7), proph (33.3)
				Total	N/A	N/A	128	NR	NR	NR	NR

(*Continued*)

Table 1. (*Continued*)

Study, Publication Year, PMID, Country	Design (Funding) (Study Years)	Risk of Bias	Eligibility Criteria	Arm	Implant Details (%) (Only Reported Details)	Reconstruction Details (%) (Only Reported Details)	N	Age (y), Mean (SD) or As Specified	Race (%)	Breast Cancer Occurrence %	Cancer Stage or Mastectomy Purpose (%)
Qureshi et al,[42] 27465177, USA	NRCS (industry) (2003–2009)	High	I: TE/IBRE: concomitant or prior ipsilateral AR; immediate implant; ADM other than AlloDerm Regenerative Tissue Matrix (LifeCell Corp., Branchburg, N.J.); concurrent congenital or acquired ipsilateral breast deformity; patients with plans for future AR	IBR with human ADM	Surface: textured (100) Shape: round (100)	Laterality: uni (53.6)/bi (46.5)Timing: imm (93.2)/del (6.8) Chemo: timing NR (47.5)Radio: timing NR (24.4)	295	49.6 (10.3)	NR	NR	NR
				IBR without human ADM	Surface: textured (100) Shape: round (100)	Laterality: uni (55.9)/bi (45)Timing: imm (83.1)/Del (16.9) Chemo: timing NR (51.7)Radio: timing NR (35.6)	118	50.8 (9.7)	NR	NR	NR
				Total	N/A	N/A	413	NR	NR	NR	NR
Safran et al,[43] 32221195, Canada	NRCS (none) (2016–2018)	High	I: immediate, direct-to-implant prepectoral IBRE: previously failed IBR; extensive skin envelope radiation damage; locally advanced breast cancer; extensive skin excision; delayed IBR or AR	IBR with human ADM	Plane: prepectoral (100)	Timing: imm (100)Stages: 1 (100)	243	NR	NR	NR	NR
				IBR without human ADM	Plane: prepectoral (100)	Timing: imm (100)Stages: 1 (100)	70	NR	NR	NR	NR
				Total	N/A	N/A	313	48.6 (11.6)	NR	NR	Ther (44.4), proph (55.6)
Seth et al,[46] 23018687, USA	NRCS (nonindustry) (2006–2008)	High	I: immediate TE/IBRE: combination of AR and TE/IBR (eg, LD flap)	IBR with human ADM	Size: mean 444.2 ml, SD 132.7 Plane: total submuscular (100)	Laterality: uni (55)/bi (45) timing: imm (100) radio: before (4.5)/after (24.6)	199 breasts	49.5 (11)	NR	NR	NR
				IBR without human ADM	Size: mean 437.3 ml, SD 132.2 Plane: total submuscular (100)	Laterality: uni (60)/bi (40) Timing: imm (100) Radio: before (6.4)/after (18.8)	293 breasts	47.4 (10.1)	NR	NR	NR
				Total	N/A	N/A	417	NR	NR	NR	NR
Sobti et al,[50] 29481386, USA	NRCS (NR) (2014–2016)	High	I: TE/IBR	IBR with human ADM	NR	Laterality: uni (25.1)/Bi (74.9) Chemo: timing NR (13.9)Radio: timing NR (9.5)	338	46.4 (9.8)	NR	NR	NR
				IBR without human ADM	NR	Laterality: uni (43.4)/Bi (56.6) Chemo: timing NR (17)Radio: timing NR (3.7)	376	46.7 (9.4)	NR	NR	NR
				Total	N/A	N/A	714	46.5 (9.6)	NR	NR	NR

(*Continued*)

Table 1. (*Continued*)

Study, Publication Year, PMID, Country	Design (Funding) (Study Years)	Risk of Bias	Eligibility Criteria	Arm	Implant Details (%) (Only Reported Details)	Reconstruction Details (%) (Only Reported Details)	N	Age (y), Mean (SD) or As Specified	Race (%)	Breast Cancer Occurrence %	Cancer Stage or Mastectomy Purpose (%)
Stein et al,[52] 32561384, Canada	NRCS (None) (2010–2019)	High	I: immediate IBR with radiation	IBR with human ADM	Size: mean 446 cm^3	Timing: imm (100) Stages: 1 (67.4)/>1 (32.6) Radiation: before (58.2)/after (41.8)	89	51.1 (NR)	NR	NR	NR
				IBR without human ADM	Size: mean 369 cm^3	Timing: imm (100) Stages: 1 (19.5)/>1 (80.5) Radiation: before (56.1)/after (43.9)	41	48.6 (NR)	NR	NR	NR
				Total	N/A	N/A	130	50.3 (NR)	NR	NR	NR
Vardanian et al,[53] 22030500, USA	NRCS (none) (2000–2008)	High	I: IBRE: delayed BR; combination of AR and TE/IBR	IBR with human ADM	NR	Laterality: uni (31)/bi (69) Timing: imm (100)	123	49 (11)	NR	NR	None (6.5), stage NR (93.5)
				IBR without human ADM	NR	Laterality: uni (39)/bi (61) Timing: imm (100)	80	47 (10)	NR	NR	None (16.3), stage 0 (83.7)
				Total	N/A	N/A	203	NR	NR	NR	NR
Weichman et al, [54] 22544088, USA	NRCS (NR) (2007–2010)	Moder-ate	I: immediate two-stage, IBRE: immediate per-manent IBR, AR, combination, or delayed BR	IBR with human ADM	NR	Timing: imm (100) Stages: >1 (100) Chemo: before (14.2)/after (31.3)/no chemotherapy (54.5) Radio: before (7.8)/after (6.4)/none (85.8)	442 breasts	51.08 (11.7)	NR	NR	Stage 0 (13.1), stage I (19.2), stage II (17.4), stage III (5.4), stage IV (0.045)
				IBR without human ADM	Plane: total submuscular (100)	Timing: imm (100) Stages: >1 (100) Chemo: before (16.7)/after (28.6)/no chemotherapy (54.7) Radio: before (8.7)/after (7.9)/none (83.4)	186 breasts	49.09 (11.58)	NR	NR	Stage 0 (18.8), stage I (18.8), stage II (17.7), stage III (8.6)
				Total	N/A	N/A	407	NR	NR	NR	NR
Woo et al,[55] 28509694, South Korea	NRCS (none) (2010–2016)	High	I: immediate TE/IBRE: direct-to-implant BR; AR; or delayed BR	IBR with human ADM	NR	Timing: imm (100) Stages: >1 (100) Chemo: after (43.2) Radio: before (3)/after (13.6)/none (83.4)	199	42.9 (6.9)	NR	NR	NR
				IBR without human ADM	Plane: total submuscular (100)	Timing: imm (100) Stages: >1 (100) Chemo: after (36.7) Radio: before (3.0)/after (16.6)/none (80.4)	199	42.8 (7.2)	NR	NR	NR
				Total	N/A	N/A	398	NR	NR	NR	NR

Laterality: whether the reconstruction was unilateral ("uni") or bilateral ("bi"). Stages: whether the reconstruction was completed in 1 stage or >1 stages. Timing: timing of reconstruction relative to mastectomy—that is, immediate ("imm") or delayed ("del"). Chemo: timing of chemotherapy relative to reconstruction.

BR, breast reconstruction; E, exclusion criteria; I, inclusion criteria; IQR, interquartile range; N/A, not applicable; NR, not reported; PMID, PubMed identifier; PMRT, postmastectomy radiation therapy; TE/I, tissue expander/implant; ther, therapeutic.

Table 2. Summary of Evidence for all Research Questions

Outcome Categories	Outcomes	IBR before versus after Radiation*	Silicone versus Saline	Prepectoral versus Total Submuscular	ADM Use versus Nonuse
Benefit/ clinical outcomes	General quality of life	nd	? No conclusion	nd	nd
	Physical well-being	~ Comparable in both groups	? No conclusion	? No conclusion	↑↓ No conclusion
	Psychosocial well-being	~ Comparable in both groups	? No conclusion	? No conclusion	↑↓ No conclusion
	Sexual well-being	~ Comparable in both groups	? No conclusion	nd	? No conclusion
	Patient satisfaction with breasts	~ Comparable in both groups	~ Comparable in both groups	? No conclusion	↑↓ No conclusion
	Patient satisfaction with surgical outcome	? No conclusion	? No conclusion	nd	nd
	Planned surgeries for reconstruction	N/P	nd	nd	nd
	Recurrence of breast cancer	N/P	N/P	N/P	N/P
	Mortality	nd	? No conclusion: silicone versus saline, and silicone versus double lumen	nd	? No conclusion
Surgical complications	Unplanned repeat hospitalization	nd	nd	nd	nd
	Duration of unplanned repeat hospitalization	nd	nd	nd	nd
	Unplanned repeat surgery for revision	? No conclusion	nd	? No conclusion	~~ Comparable in both groups
	Unplanned repeat surgery for complications	nd	nd	nd	? No conclusion
	Pain	? No conclusion	nd	↑↓ No conclusion	↑↓ No conclusion
	Analgesic use	nd	nd	? No conclusion	? No conclusion
	Necrosis	? No conclusion	nd	? No conclusion	~ Comparable in both groups: adjOR 0.89 (95% CI 0.63–1.25); 4 studies
	Animation deformity	nd	nd	nd	nd
	Implant-related infections	nd	nd	nd	nd
	Implant rupture	nd	nd	nd	? No conclusion
	Implant deflation	nd	nd	nd	nd
	Implant malposition	nd	nd	nd	? No conclusion
	Implant failure/loss or need for explant surgery	~~ Comparable in both groups (adjOR 0.87, 95% CI 0.62–1.24; 3 NRCSs)	? No conclusion	? No conclusion	◆◆ with ADM: adjOR 1.28 (95% CI 0.97–1.70); 6 studies
	Capsular contracture	N/P	? No conclusion	? No conclusion	↑↓ No conclusion
	New neoplasms	N/A	nd	nd	nd
	Complications that delay other cancer treatments	nd	nd	nd	nd
	Thromboembolic events	nd	nd	nd	? No conclusion
	Infections not explicitly implant-related	N/P	.	~ Comparable for prepectoral versus total submuscular	◆ with ADM use: adjOR 1.56 (95% CI 0.96–2.53); 7 studies
	Wound dehiscence	N/P	N/P	N/P	↑↓ No conclusion
	Delayed healing	N/P	N/P	N/P	? No conclusion
	Seroma	? No conclusion	nd	? No conclusion	~~ Comparable in both groups: adjOR 1.52 (95% CI 0.62 to 3.71); 4 studies
	Chronic conditions	N/P	nd	nd	N/P
	Touch sensitivity	N/P	N/P	N/P	N/P
	Scarring	N/P	N/P	N/P	N/P
	Red breast syndrome	.	N/P	N/P	N/P

All reported effect sizes are from meta-analyses. Color legend: Grey = Insufficient strength of evidence, Pink = Low strength of evidence, Blue = Moderate strength of evidence, Green = High strength of evidence (no instances in this table).

*No evidence addressed timing of IBR or AR relative to chemotherapy or timing of AR relative to radiation. ▲ = low SoE of better benefit/clinical outcomes; ▲▲ = moderate SoE of better benefit/clinical outcomes (no instances in this table); ▲▲▲ = high SoE of better benefit/clinical outcomes (no instances in this table) ◆ = low SoE of increased complications; ◆◆ = moderate SoE of increased complications; ◆◆◆ = high SoE of increased complications (no instances in this table); ~ = low SoE of comparable outcomes; ~~ = moderate SoE of comparable outcomes; ~~~ = high SoE of comparable outcomes (no instances in this table); ? = insufficient strength of evidence due to sparse evidence; ↑↓ = insufficient strength of evidence due to inconsistent or conflicting results; = not applicable (ie, outcome not applicable to research question).

N/P, not prioritized (for strength of evidence assessment); nd, no data (no evidence identified); TRAM, transverse rectus abdominis myocutaneous.

(95% CI −11.0 to 3.23) for satisfaction with breasts (MCID = 5[58]). Cordeiro et al[21] did not report adjusted effect sizes but reported no statistically significant between-group differences for physical well-being and satisfaction with breasts. For psychosocial well-being and sexual well-being, Cordeiro et al[21] reported on only statistical significance of MDs ($P < 0.01$); the unadjusted MDs (−1.2 for psychosocial well-being and −1.4 for sexual well-being) were smaller than their MCIDs. Likewise, Cordeiro et al[21] reported a statistically significant different adjMD for satisfaction with surgical outcome ($P = 0.02$), but the unadjusted MD (−1.8) was less than the MCID (5[58]).

Surgical complications: Four NRCSs reported on surgical complications, which were generally comparable regardless of timing. Three NRCSs reported on the risk of implant loss/failure or need for explantation at 3.3–3.6 years. Effect sizes ranged from a statistically significant 0.62, favoring before radiation, to a nonsignificant 1.12, yielding a summary effect size of 0.87 (95% CI 0.62–1.24; $I^2 = 54\%$) (Fig. 2).

One NRCS (Yoon et al[56]) reported that 2-year followup data for pain interference (using the Patient-Reported Outcomes Measurement Information System; 100-point scale; higher is better; MCID = 4.5[59]) were comparable irrespective of whether before or after radiation (adjMD = 2.86, 95% CI −1.05 to 6.77) (**See table 4-1, Supplemental Digital Content 4**, **http://links.lww.com/PRSGO/B953**). Although no adjusted effect sizes were reported, Yoon et al[56] reported that 2-year risks of five other complications were also comparable between treatment groups: major infections (requiring treatment with intravenous antibiotics) ($P = 0.40$), minor infections (treated with oral antibiotics) ($P = 0.96$), wound dehiscence ($P = 0.32$), seroma ($P = 0.46$), and capsular contracture ($P = 0.80$) (**See table 4-2, Supplemental Digital Content 4**, **http://links.lww.com/PRSGO/B953**). One NRCS (Eriksson et al[23]) reported comparable risks of unplanned repeat surgeries for revision [adjusted hazard ratio (adjHR) = 0.94, 95% CI 0.63–1.40]. Another NRCS (Hirsch et al[26]) reported comparable risks of necrosis [adjusted OR (adjOR) = 0.96, 95% CI 0.68 to 1.35].

Materials

Five NRCSs,[14,21,30,35,36] but no RCTs, compared implant materials in 2929 patients (between 143 and 1143 patients each) (Table 1). All five NRCSs had a high risk of bias. In Le et al[30] (in USA), the large majority (94%) were White, and in Macadam et al[35] (in Vancouver, Canada), a majority (66%) were Asian; the other studies did not report on race.

Silicone versus Saline Implants

Benefit/Clinical Outcomes: Macadam et al[35] used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 to report on general quality of life and BREAST-Q to report on physical well-being, psychosocial well-being, sexual well-being, and satisfaction with outcome (**See table 4-3, Supplemental Digital Content 4**, **http://links.lww.com/PRSGO/B953**). There was a statistically significant difference in psychosocial well-being ($P = 0.03$), but not for the other outcomes ($P = 0.13$ for quality-of-life, $P = 0.28$ for physical well-being, $P = 0.056$ for sexual well-being, and $P = 0.082$ for satisfaction with outcome). No adjusted effect sizes were reported.

Two NRCSs (Macadam et al[35] and McCarthy et al[36]) reported on satisfaction with breasts (using the BREAST-Q; MCID = 5[58]). McCarthy et al[36] reported clinically comparable satisfaction at 2.4–3.3 years (adjMD = 4.1, 95% CI 1.31–6.89). Macadam et al[36] reported a statistically significant between-group difference ($P = 0.008$), but no adjusted effect size was reported.

One NRCS (Le et al[30]) reported comparable risks of breast cancer mortality (adjHR = 1.01, 95% CI 0.44–2.34) and nonbreast cancer mortality (adjHR = 1.75, 95% CI 0.29–10.34) between silicone and saline groups at 12.4 years of followup (**See table 4-4, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**).

Surgical Complications: Two NRCSs (Cordeiro et al[21] and Antony et al[14]) reported on surgical complications (**See table 4-4, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**). Cordeiro et al[21] reported that risk of implant failure/loss was lower among patients with silicone implants (adjOR = 0.61, 95% CI 0.36–1.07). Antony et al[14] reported no statistically significant difference in risks of capsular contracture, but no adjusted effect size or *P* value was reported.

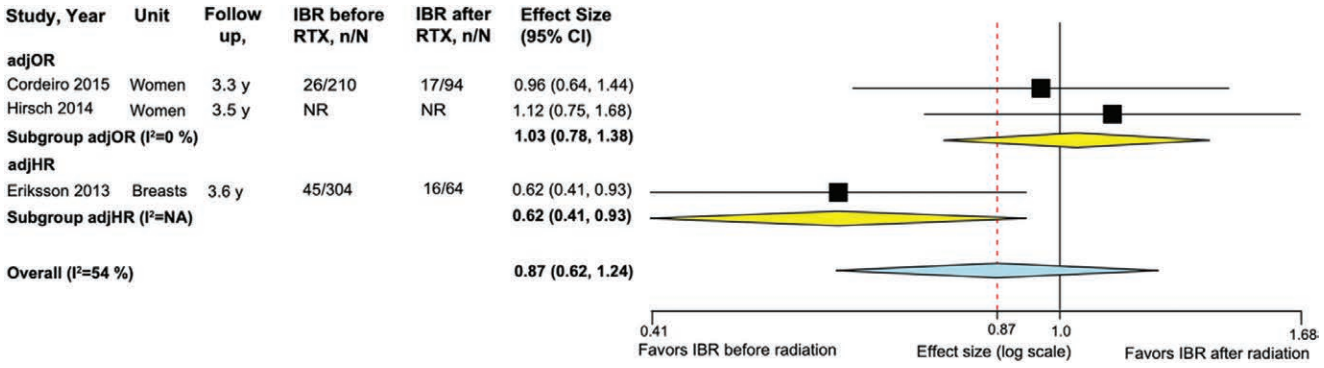

Fig. 2. Meta-analysis for timing of IBR relative to radiation (Outcome: Implant failure/loss or need for explant surgery). Abbreviations: adj = adjusted, CI = confidence interval, HR = hazard ratio = IBR = implant-based reconstruction, I2 = measure of statistical heterogeneity (% of total variability that is due to between-study variability), NR = not reported, OR = odds ratio, RTX = radiation therapy, y = years.

Double-lumen Implants

One NRCS (Le et al[30]) reported comparable risks of breast cancer mortality at 12.4 years of follow-up between silicone and double-lumen implants (adjHR = 1.49, 95% CI 0.83–2.70) (**See table 4-4, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**.) However, non-breast cancer mortality was higher among patients with double-lumen implants (adjHR = 3.13, 95% CI 0.91–10.78). No study addressed surgical complications. No study compared saline and double-lumen implants.

Anatomic Planes

We included eight studies (one RCT,[11] and seven NRCSs reported in eight articles[15,16,18,24,28,29,38,39]) that compared prepectoral, partial submuscular, and total submuscular planes of implant placement in 1555 patients. We rated the RCT as having a moderate risk of bias, six of the seven NRCSs at a high risk, and one NRCS at a moderate risk. No study reported on race. Studies followed patients between 6 months and 6.1 years.

Prepectoral versus Total Submuscular Placement of Implants

Benefit Outcomes: One NRCS (Cattelani et al[18]) reported on physical well-being using both the Constant Murley score at 7 days and the Disabilities of the Arm, Shoulder, and Hand instrument at 1 year; psychosocial well-being based on number of days until return to usual work; and satisfaction with breasts using the BREAST-Q (**See table 4-5, Supplemental Digital Content 4**, **http://links.lww.com/PRSGO/B953**.) Although no adjusted effect sizes were reported, patients with prepectoral implants fared statistically significantly better than patients with total submuscular implants (adjusted $P < 0.001$ for each outcome).

Surgical Complications: Two NRCSs (Nealon et al[37] and Kraenzlin et al[29]) reported comparable risks of infections. (**See table 4-6, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**.) Nealon et al[37] reported an imprecise adjOR of 0.31 (95% CI <0.01–8.65) and Kraenzlin et al[29] reported a P value of 0.21 (no adjusted effect size reported).

Although no adjusted effect sizes were reported, two NRCSs (Avila et al[15] and Cattelani et al[18]) reported inconsistent results regarding pain (**See table 4-5, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**). Avila et al[15] used a visual analog scale (VAS) and reported no statistically significantly difference in pain levels. However, Cattelani et al[18] used the Brief Pain Inventory-Short Form (BPI-SF) and reported that patients with total submuscular implants had clinically and statistically significantly lower pain 7 days after surgery ($P < 0.001$; no adjusted effect size reported).

Other complications were reported by one NRCS each. Avila et al[15] reported lower analgesic use with prepectoral implants ($P = 0.03$; no adjusted effect size reported). Avila et al[15] also reported comparable risk of unplanned repeat surgeries for revision (P = NS), although no adjusted effect size was reported. Nealon et al[37] reported comparable risks of necrosis (adjOR = 1.01, 95% CI 0.74–5.95), explantation (adjOR = 1.01, 95% CI 0.07 to 14.1), capsular contracture (adjOR = 0.30, 95% CI 0.03 to 1.55), and seroma (adjOR = 1.49, 95% CI 0.37–6.11).

Prepectoral versus Partial Submuscular Placement of Implants

Benefit Outcomes: One RCT (Lee et al[11]) reported that patients with prepectoral or partial submuscular implants had comparable physical well-being measured using the physical component of the SF-36 (0–100; MCID not available) (MD = 0.0, 95% CI −5.0 to 5.0) and comparable psychosocial well-being using the anxiety and depression components of the Hospital Anxiety and Depression Scale (0–21 scale; MCIDs not available) (anxiety MD = 0.0, 95% CI −7.5 to 7.5; depression MD = 1.2, 95% CI −3.2 to 5.6) (**See table 4-4, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**).

Surgical Complications: Specific complications were reported by one study each. One NRCS (Kim and Hong[28]) reported comparable pain using the VAS (0–10; MCID = 2[60]) (adjMD = −0.12; $P = 0.12$) (**See table 4-5, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**). The RCT (Lee et al[11]) reported comparable risks of seroma (OR = 1.06, 95% 0.15–7.34) and capsular contracture (5% versus 0%; effect size not calculable). (**See table 4-6, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953** .)

Use versus Nonuse of ADMs

We included 22 studies (two RCTs,[12,13] and 20 NRCSs reported in 29 articles[12,13,17–20,22,25–27,31–34,37,40–43,45–48,50–55]) of human ADM use in 43,334 patients (between 36 and 18,977 patients each) (Table 1). Among the 14 of 22 studies that reported funding information, eight explicitly stated that they were not funded, five were funded by non-industry sources (eg, federal sources, foundations), and one was funded by industry (Lifecell Corporation).

One RCT had a high risk of bias and the other moderate risk. Fifteen NRCSs had a high risk of bias, four moderate risk, and one low risk. Studies followed patients between 2 and 5 years.

Benefit/Clinical Outcomes: One RCT and two NRCSs reported on benefit/clinical outcomes (**See table 4-7, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**). All three studies reported on physical well-being, but the results were inconsistent. Comparable physical well-being (measured by the BREAST-Q; MCID = 3[58]) regardless of ADM use was reported by one RCT (McCarthy et al[12]: NMD = 0.50, 95% CI −5.93 to 6.93) and one NRCS (Ganesh Kumar et al[25]: adjMD = −0.82, 95% CI −3.01 to 1.37). However, the other NRCS (Cattelani et al[18]) reported that patients with ADMs had better unadjusted Constant Murley and Disabilities of the Arm, Shoulder, and Hand (DASH) physical well-being scores ($P < 0.001$ for both); no adjusted effect sizes were reported.

Two NRCSs reported inconsistent results for psychosocial well-being. Ganesh Kumar et al[25] reported comparable BREAST-Q scores (MCID = 4[58]) regardless of ADM use (adjMD = −0.26, 95% CI −2.97 to 2.45). On the other hand, Cattelani et al[18] reported that patients with ADMs

returned to work considerably sooner than who had not (mean 35 versus 57 days, $P < 0.001$). The same two NRCSs also reported inconsistent results on sexual well-being using the BREAST-Q (MCID 5 points[58]). Ganesh Kumar et al[25] reported comparable scores (adjMD = −1.95, 95% CI −4.96 to 1.06), but Cattelani et al,[18] without mentioning an adjusted effect size, reported that patients with ADMs had considerably higher unadjusted scores ($P < 0.001$).

One NRCS (Ganesh Kumar et al[25]) reported on sexual well-being using the BREAST-Q (MCID = 5[58]), which was comparable with or without ADM use (adjMD = −2.28, 95% CI −5.63 to 1.06).

Surgical Complications: All 22 studies reported on surgical complications.

Across six NRCSs, the summary adjOR for implant failure/loss or need for explantation was 1.28 (95% CI 0.97–1.70; I^2 = 16%) (Fig. 3A). Across seven studies (two RCTs and five NRCSs), the summary adjOR for infections was 1.56 (95% CI 0.96–2.53; I^2 = 46%) (Fig. 3B), with similar findings among the RCTs and the NRCSs (P = 0.44, based on a meta-regression). Across four NRCSs, the summary adjOR for necrosis was 0.89 (95% CI 0.63–1.25; I^2 = 25%) (Fig. 4A). Across four studies (one RCT and three NRCSs), the summary adjOR for seroma was 1.52 (95% CI 0.62–3.71; I^2 = 52%) (Fig. 4B), with no significant difference between the RCT and the NRCSs (P = 0.30, based on a meta-regression). Other studies that reported on these outcomes did not report sufficient data for inclusion in meta-analyses.

Three NRCSs reported comparable risks of unplanned repeat surgeries for revision of reconstruction (**See table 4-8, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**), but insufficient data were reported to allow meta-analysis. Ibrahim et al[27] reported that, at 6 months, risks were comparable regardless of whether ADMs were used (P = 0.14; no adjusted effect size reported). At approximately 5 years, no significant between-group differences in risk of unplanned repeat surgeries were reported by Nealon et al[38] (adjOR = 0.86, 95% CI 0.69–1.08) and Sobti et al[50] (adjOR = 1.10, 95% CI 0.63–1.92).

Results were inconsistent across studies for various complications. One RCT and one NRCS reported on pain (**See table 4-9, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**). The RCT (McCarthy et al[12]) reported that ADM use was associated with greater pain in the first 24 hours (VAS 0–100 scale: NMD = 6.2, 95% CI −4.9 to 17.3; MCID = 5[61]) and during expansion (NMD = 6.8, 95% CI 1.1–12.5) but not after expansion (NMD = −4.6, 95% CI −9.8 to 0.6). However, the NRCS (Cattelani et al[18]) reported statistically significantly less pain in the ADM group 7 days after surgery on the BPI-SF scale ($P < 0.001$; no adjusted effect size reported).

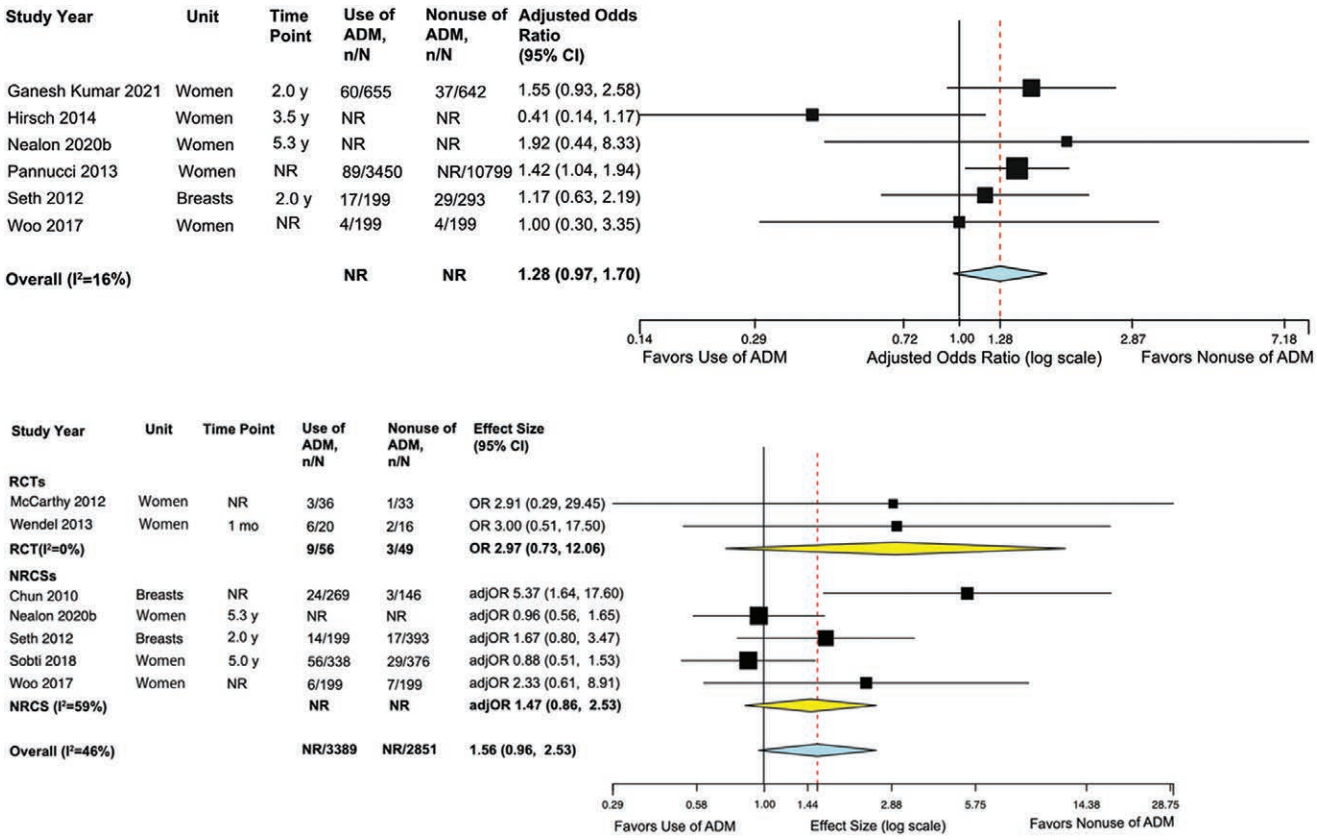

Fig. 3. Meta-analyses for ADM use during IBR: A, Outcome: implant failure/loss or need for explant surgery. B, Outcome: infections. Abbreviations: ADM = acellular dermal matrix, CI = confidence interval, IBR = implant-based reconstruction, I2 = measure of statistical heterogeneity (% of total variability that is due to between-study variability), mo = months, NR = not reported, NRCS = nonrandomized comparative study, OR = odds ratio, RCT = randomized controlled trial, y = years.

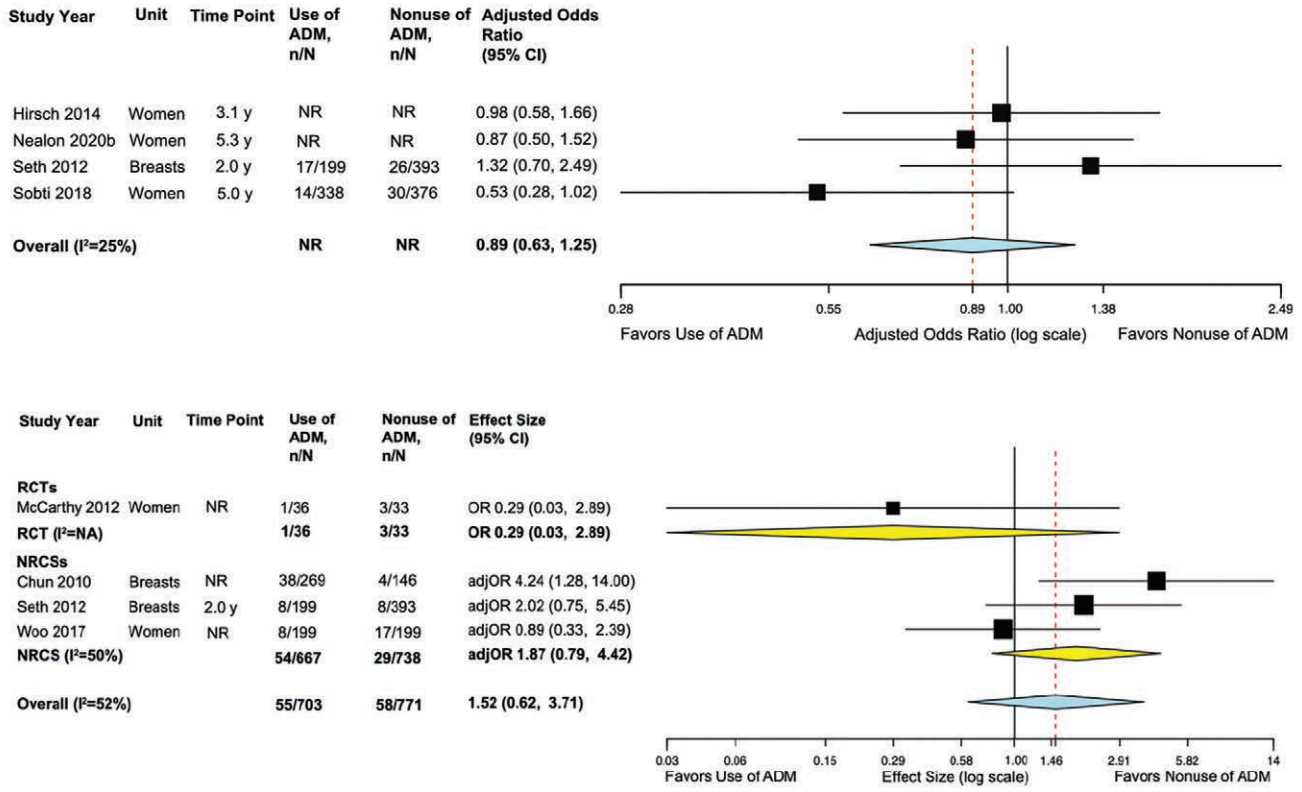

Fig. 4. Meta-analyses for ADM use during IBR: A, Outcome: necrosis. B, Outcome: Seroma. Abbreviations: ADM = acellular dermal matrix, CI = confidence interval, IBR = implant-based reconstruction, I2 = measure of statistical heterogeneity (% of total variability that is due to between-study variability), NR = not reported, OR = odds ratio.

Two NRCSs reported inconsistent results on implant malposition (**See table 4-8, Supplemental Digital Content 4**, **http://links.lww.com/PRSGO/B953**). Ganesh Kumar et al[25] reported that risks were comparable (P = 0.83; no adjusted effect size reported), but Vardanian et al[53] reported that ADM use was associated with a lower risk (adjOR = 0.23, 95% CI 0.06–0.78).

Four NRCSs reported inconsistent results on capsular contracture (**See table 4-8, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**). Three NRCSs reported comparable risks (Ganesh Kumar et al[25]: P = 0.24; Nealon et al[38]: adjOR = 0.78, 95% CI 0.46–1.36; and Sobti et al[50]: adjOR = 0.57, 95% CI 0.23–1.43). However, Vardanian et al[53] reported that ADM use was associated with a lower risk (adjOR = 0.18, 95% CI 0.08–0.43). We do not report a meta-analysis for this outcome due to substantial statistical heterogeneity (ie, marked between-study variability in results, as suggested by an I^2 of 85%).

Four NRCSs reported inconsistent results on wound dehiscence. (**See table 4-8, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**.) ADM use was associated with a greater risk in one NRCS (Ganesh Kumar et al[25]: P = 0.009), a comparable risk in another NRCS (Ibrahim et al[27]: P = 0.26), and a lower risk in a third NRCS (Qureshi et al[42]: adjOR = 0.4; P < 0.05). The fourth NRCS (Craig et al[22]) reported adjusted data only for the subgroup of patients who did not receive postoperative radiation; ADM use was associated with a greater risk (adjOR 2.46, 95% CI 1.23–4.93).

Various complications were reported by one study each. One RCT (McCarthy et al[12]) reported comparable analgesic use within the first 24 hours (MD = −134 mg oral codeine equivalents, 95% CI −440 to 172) (**See table 4-9, Supplemental Digital Content 4**, **http://links.lww.com/PRSGO/B953**). One NRCS (Woo et al[55]) reported comparable risk of delayed healing (adjOR = 1.41, 95% CI 0.67–2.96) (**See table 4-8, Supplemental Digital Content 4, http://links.lww.com/PRSGO/B953**). One NRCS each reported no statistically significant differences in risk of thromboembolic events (Ibrahim et al[27]) or implant rupture (Ganesh Kumar et al[25]), although no adjusted effect sizes were reported. However, Peled et al[41] reported a statistically significant lower risk of unplanned repeat surgeries for complications in patients with ADM use (P < 0.05), but no adjusted effect size was reported.

DISCUSSION

The current evidence does not suggest clearly preferred modalities for IBR after breast-cancer-related mastectomy. We found no evidence regarding timing vis-a-vis chemotherapy. This may be related to the preference of clinicians to base decisions regarding timing of chemotherapy on the severity of the underlying cancer. Limited evidence suggests that timing before or after radiation may not affect physical well-being, psychosocial well-being, sexual well-being, and patient satisfaction with breasts, and probably does not affect implant failure/loss or explantation. Weak evidence suggests clinically comparable satisfaction with

breasts after silicone or saline implants, but the evidence is insufficient to make conclusions comparing surgical complications. There is insufficient evidence regarding double-lumen implants. Evidence was also largely insufficient regarding choice of anatomic plane of implant placement. The evidence is also weak for whether the implant should be placed in the prepectoral, total submuscular, or partial submuscular planes. However, prepectoral and total submuscular placements may be associated with comparable risks of infections. Regarding ADMs, there is insufficient evidence whether they impact patient-reported outcomes. However, ADM use may be associated with some surgical complications, such as infections and implant failure, but not others, such as necrosis and seroma. Our findings that ADM use may be associated with infections and implant failure are consistent with a recent U.S. Food and Drug Administration Safety Communication regarding ADM use.[62]

Given the relatively weak evidence addressing some key decisions in clinical practice and the highly patient preference-sensitive nature of the decisions,[63,64] we encourage clinicians to inform patients about the limitations of existing research. Among the limitations is that very little research has focused on patients whose mastectomy was performed for prophylactic (and not therapeutic) purposes. Therefore, the patient's values and preferences and the clinician's expertise and experience are highly important.

Strengths and Limitations

We followed contemporary methodological standards for SRs, including multi-stakeholder engagement and use of state-of-the-art methods for searching, screening, assessing risk of bias, extracting and synthesizing data, and assessing SoE.

A few limitations to the evidence base are worth noting. Only three of 36 included studies were RCTs, each small. Most studies were at a moderate or high risk of bias, primarily because participants, care providers, and/or outcome assessors were not blinded, and/or outcome data were incomplete. Studies commonly reported incomplete data regarding adjusted analyses, often reporting only adjusted *P* values without adjusted effect sizes. Furthermore, comparisons of subgroups were limited in that none of the studies reported statistical analyses of differences between subgroups or, what would have been preferable, evidence of treatment effect heterogeneity. Finally, 80% of studies were conducted in North America (USA or Canada), with some studies from South Korea or Europe. It is unclear to what extent the evidence applies to populations that are not mostly White, middle-aged, nonobese women located in North America. However, the interventions examined in the studies are mostly reflective of available interventions in the USA, such as silicone and saline implants, human ADMs, and prepectoral and total submuscular placements of implants.

Implications for Research

Research is needed to address various questions, especially timing, materials, and anatomic planes. Given the recent increase in prophylactic mastectomies[65–69] and because the risk-benefit tradeoffs may be different from those for women undergoing therapeutic mastectomies, future studies should enroll, and separately report data for, women undergoing prophylactic mastectomies. In addition, studies should enroll more diverse groups of women, particularly by race, ethnicity, age, and socioeconomic position.

It is also important that, when possible, future studies conduct randomization to avoid selection bias. If randomization is not feasible or practical, as may often be the case for surgical topics,[70] studies (such as those using data from the Tracking Operations and Outcomes for Plastic Surgeons registry[71]) should fully report between-group estimates of treatment effect that conduct adequate statistical adjustment analyses to account for important confounders, including at least age, race/ethnicity, weight, and breast cancer stage. Ideally, propensity score analyses (or similar rigorous techniques) should be used to adequately adjust for confounders. Future studies should also evaluate important outcomes that are not sufficiently reported in the identified evidence, including quality of life, number of planned surgeries for reconstruction, incidence and duration of unplanned repeat hospitalizations and surgeries, analgesic use, animation deformity, and complications that may delay other cancer-related treatments.

CONCLUSIONS

The current evidence base allows few conclusions, tempered by the low-to-moderate SoE, for the comparative benefits and harms of IBR-related modalities for women who have undergone mastectomy for breast cancer. IBR before or after radiation may result in comparable benefit outcomes and probably results in a comparable risk of implant failure/loss or explantation. Silicone or saline implants may result in comparable patient satisfaction with breasts, but the evidence for surgical complications is insufficient. Whether the implant is placed in the prepectoral or total submuscular plane may result in comparable risk of infections, but the evidence for beneficial outcomes is insufficient. Regarding human ADM use, the evidence for beneficial outcomes is insufficient, but its use may be associated with greater risks of implant failure/loss or explantation and infections but comparable risks of necrosis and seroma. More research is needed to identify effective and safe surgical options for IBR for women who have undergone mastectomy for treatment or prophylaxis against breast cancer.

Ian J. Saldanha, MBBS, MPH, PhD
Center for Evidence Synthesis in Health
Department of Health Services, Policy, and Practice
Brown University School of Public Health
121 S. Main Street, Box G-121-8
Providence, RI 02903
E-mail: ian_saldanha@brown.edu

ACKNOWLEDGMENTS

We thank Binita Ashar, MD; Katelyn Donnelly, MPH; Phyllis Greenberger, MSW; Michele Manahan, MD; Priscilla McAuliffe, MD, PhD; Steven Nagel, MD; William Sikov, MD; Terence Myckatyn, MD; Anne Taylor, MD; Myelin Torres, MD; Edwin Wilkins, MD; and Sung Yoon, MD, who served as key

informants and/or technical experts and helped us refine the research questions and develop the protocol. We are also grateful to the project's Task Order Officer Jill Huppert, MD, MPH and the Acting EPC Program Director Christine Chang, MD, MPH at the Agency for Healthcare Research and Quality, Rockville, Maryland, and to the full systematic review report's peer reviewers and Associate Editor Timothy Wilt, MD, MPH, at the Minnesota Evidence-based Practice Center, Minneapolis, Minnesota. We also thank Kristin Konnyu, MSc, PhD and Jonah Popp, PhD for their careful study screening and related contributions to the project. The authors of this study are responsible for its content. Statements in the report should not be construed as endorsement by AHRQ or Department of Health and Human Services. AHRQ retains a license to display, reproduce, and distribute the data and the report from which this article was derived under the terms of the agency's contract with the author. This systematic review was prospectively registered through PROSPERO (Registration Number: CRD42020193183).

REFERENCES

1. Jonczyk MM, Jean J, Graham R, et al. Surgical trends in breast cancer: a rise in novel operative treatment options over a 12 year analysis. *Breast Cancer Res Treat.* 2019;173:267–274.
2. American Society of Plastic Surgeons. 2019 plastic surgery statistics report. Available at https://www.plasticsurgery.org/documents/News/Statistics/2019/plastic-surgery-statistics-report-2019.pdf. Accessed February 13, 2021.
3. Saldanha IJ, Cao W, Broyles JM, et al. Breast Reconstruction after Mastectomy: A Systematic Review and Meta-Analysis. Comparative Effectiveness Review No. 245. Rockville, Md.: Agency for Healthcare Research and Quality; 2021. Available at https://doi.org/10.23970/AHRQEPCCER245. Accessed July 16, 2021.
4. Saldanha IJ, Broyles JM, Adam GP, et al. Autologous breast reconstruction after mastectomy for breast cancer: a systematic review. *Plast Reconstr Surg.* 2022; in press.
5. Broyles JM, Balk EM, Adam GP, et al. Implant-based breast reconstruction versus autologous reconstruction after mastectomy for breast cancer: a systematic review and meta-analysis. *Plast Reconstr Surg.* 2022; in press.
6. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol.* 2015;68:1312-1324.
7. Higgins JP, Altman DG, Gøtzsche PC, et al.; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
8. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919.
9. Gerrity M, Fiordalisi C, Pillay J, et al. AHRQ methods for effective health care. Roadmap for Narratively Describing Effects of Interventions in Systematic Reviews. Rockville, Md.: Agency for Healthcare Research and Quality (US); 2020.
10. Murad MH, Fiordalisi C, Pillay J, et al. Making narrative statements to describe treatment effects. *J Gen Intern Med.* 2021;36:196–199.
11. Lee JS, Park E, Lee JH, et al. A prospective comparison study of early functional outcomes after implant-based breast reconstruction: subpectoral versus prepectoral technique. *Ann Palliat Med.* 2021;10:2520–2529.
12. McCarthy CM, Lee CN, Halvorson EG, et al. The use of acellular dermal matrices in two-stage expander/implant reconstruction: a multicenter, blinded, randomized controlled trial. *Plast Reconstr Surg.* 2012;130(5 Suppl 2):57S–66S.
13. Wendel J. *Use of Dermal Matrix in Breast Reconstruction.* ClinicalTrials.gov. 2013. Available at https://clinicaltrials.gov/ct2/show/study/NCT00692692. Accessed April 20, 2021.
14. Antony AK, McCarthy C, Disa JJ, et al. Bilateral implant breast reconstruction: outcomes, predictors, and matched cohort analysis in 730 2-stage breast reconstructions over 10 years. *Ann Plast Surg.* 2014;72:625–630.
15. Avila A, Bartholomew AJ, Sosin M, et al. Acute postoperative complications in prepectoral versus subpectoral reconstruction following nipple-sparing mastectomy. *Plast Reconstr Surg.* 2020;146:715e–720e.
16. Bozzuto LM, Bartholomew AJ, Tung S, et al. Decreased postoperative pain and opioid use following prepectoral versus subpectoral breast reconstruction after mastectomy: a retrospective cohort study: pain after pre- versus subpectoral reconstruction. *J Plast Reconstr Aesthet Surg.* 2021;74:1763–1769.
17. Brooke S, Mesa J, Uluer M, et al. Complications in tissue expander breast reconstruction: a comparison of AlloDerm, DermaMatrix, and FlexHD acellular inferior pole dermal slings. *Ann Plast Surg.* 2012;69:347–349.
18. Cattelani L, Polotto S, Arcuri MF, et al. One-step prepectoral breast reconstruction with dermal matrix-covered implant compared to submuscular implantation: functional and cost evaluation. *Clin Breast Cancer.* 2018;18:e703–e711.
19. Chun YS, Verma K, Rosen H, et al. Implant-based breast reconstruction using acellular dermal matrix and the risk of postoperative complications. *Plast Reconstr Surg.* 2010;125:429–436.
20. Clarke-Pearson EM, Lin AM, Hertl C, et al. Revisions in implant-based breast reconstruction: how does direct-to-implant measure up? *Plast Reconstr Surg.* 2016;137:1690–1699.
21. Cordeiro PG, Albornoz CR, McCormick B, et al. What is the optimum timing of postmastectomy radiotherapy in two-stage prosthetic reconstruction: radiation to the tissue expander or permanent implant? *Plast Reconstr Surg.* 2015;135:1509–1517.
22. Craig ES, Clemens MW, Koshy JC, et al. Outcomes of acellular dermal matrix for immediate tissue expander reconstruction with radiotherapy: a retrospective cohort study. *Aesthet Surg J.* 2019;39:279–288.
23. Eriksson M, Anveden L, Celebioglu F, et al. Radiotherapy in implant-based immediate breast reconstruction: risk factors, surgical outcomes, and patient-reported outcome measures in a large Swedish multicenter cohort. *Breast Cancer Res Treat.* 2013;142:591–601.
24. Gabriel A, Sigalove S, Storm-Dickerson TL, et al. Dual-plane versus prepectoral breast reconstruction in high-body mass index patients. *Plast Reconstr Surg.* 2020;145:1357–1365.
25. Ganesh Kumar N, Berlin NL, Kim HM, et al. Development of an evidence-based approach to the use of acellular dermal matrix in immediate expander-implant-based breast reconstruction. *J Plast Reconstr Aesthet Surg.* 2021;74:30–40.
26. Hirsch EM, Seth AK, Kim JYS, et al. Analysis of risk factors for complications in expander/implant breast reconstruction by stage of reconstruction. *Plast Reconstr Surg.* 2014;134:692e–699e.
27. Ibrahim AMS, Shuster M, Koolen PGL, et al. Analysis of the National Surgical Quality Improvement Program database in 19,100 patients undergoing implant-based breast reconstruction: complication rates with acellular dermal matrix. *Plast Reconstr Surg.* 2013;132:1057–1066.
28. Kim JH, Hong SE. A comparative analysis between subpectoral versus prepectoral single stage direct-to-implant breast reconstruction. *Medicina (Kaunas).* 2020;56:E537.
29. Kraenzlin F, Darrach H, Khavanin N, et al. Tissue expander-based breast reconstruction in the prepectoral versus subpectoral plane: An analysis of short-term outcomes. *Ann Plast Surg.* 2021;86:19–23.

30. Le GM, O'Malley CD, Glaser SL, et al. Breast implants following mastectomy in women with early-stage breast cancer: prevalence and impact on survival. *Breast Cancer Res.* 2005;7:R184–R193.
31. Lee KT, Bang SI, Pyon JK, et al. Method of breast reconstruction and the development of lymphoedema. *Br J Surg.* 2017;104:230–237.
32. Lee KT, Lee H, Jeon BJ, et al. Impact of overweight/obesity on the development of hematoma following tissue expander-based breast reconstruction. *J Plast Reconstr Aesthet Surg.* 2020;74:307–315.
33. Lee KT, Pyon JK, Bang SI, et al. Does the reconstruction method influence development of mastectomy flap complications in nipple-sparing mastectomy? *J Plast Reconstr Aesthet Surg.* 2013;66:1543–1550.
34. Liu AS, Kao HK, Reish RG, et al. Postoperative complications in prosthesis-based breast reconstruction using acellular dermal matrix. *Plast Reconstr Surg.* 2011;127:1755–1762.
35. Macadam SA, Ho AL, Cook EF Jr, et al. Patient satisfaction and health-related quality of life following breast reconstruction: patient-reported outcomes among saline and silicone implant recipients. *Plast Reconstr Surg.* 2010;125:761–771.
36. McCarthy CM, Klassen AF, Cano SJ, et al. Patient satisfaction with postmastectomy breast reconstruction: a comparison of saline and silicone implants. *Cancer.* 2010;116:5584–5591.
37. Nealon KP, Sobti N, Gadd M, et al. Assessing the additional surgical risk of contralateral prophylactic mastectomy and immediate breast implant reconstruction. *Breast Cancer Res Treat.* 2020;179:255–265.
38. Nealon KP, Weitzman RE, Sobti N, et al. Prepectoral direct-to-implant breast reconstruction: safety outcome endpoints and delineation of risk factors. *Plast Reconstr Surg.* 2020;145:898e–908e.
39. Ozgur I, Kurul S, Bademler S, et al. Comparison of subpectoral versus dual-plane implant based immediate breast reconstruction after nipple-areola sparing mastectomy. *Ann Chir Plast Esthet.* 2021;66:447–458.
40. Pannucci CJ, Antony AK, Wilkins EG. The impact of acellular dermal matrix on tissue expander/implant loss in breast reconstruction: an analysis of the tracking outcomes and operations in plastic surgery database. *Plast Reconstr Surg.* 2013;132:1–10.
41. Peled AW, Foster RD, Garwood ER, et al. The effects of acellular dermal matrix in expander-implant breast reconstruction after total skin-sparing mastectomy: results of a prospective practice improvement study. *Plast Reconstr Surg.* 2012;129:901e–908e.
42. Qureshi AA, Broderick KP, Belz J, et al. Uneventful versus successful reconstruction and outcome pathways in implant-based breast reconstruction with acellular dermal matrices. *Plast Reconstr Surg.* 2016;138:173e–183e.
43. Safran T, Al-Halabi B, Viezel-Mathieu A, et al. Direct-to-implant, prepectoral breast reconstruction: a single-surgeon experience with 201 consecutive patients. *Plast Reconstr Surg.* 2020;145:686e–696e.
44. Santosa KB, Chen X, Qi J, et al. Postmastectomy radiation therapy and two-stage implant-based breast reconstruction: is there a better time to irradiate? *Plast Reconstr Surg.* 2016;138:761–769.
45. Seth AK, Hirsch EM, Fine NA, et al. Additive risk of tumescent technique in patients undergoing mastectomy with immediate reconstruction. *Ann Surg Oncol.* 2011;18:3041–3046.
46. Seth AK, Hirsch EM, Fine NA, et al. Utility of acellular dermis-assisted breast reconstruction in the setting of radiation: a comparative analysis. *Plast Reconstr Surg.* 2012;130:750–758.
47. Seth AK, Hirsch EM, Kim JY, et al. Two surgeons, one patient: the impact of surgeon-surgeon familiarity on patient outcomes following mastectomy with immediate reconstruction. *Breast.* 2013;22:914–918.
48. Seth AK, Hirsch EM, Kim JY, et al. Hematoma after mastectomy with immediate reconstruction: an analysis of risk factors in 883 patients. *Ann Plast Surg.* 2013;71:20–23.
49. Seth AK, Hirsch EM, Kim JYS, et al. Long-term outcomes following fat grafting in prosthetic breast reconstruction: a comparative analysis. *Plast Reconstr Surg.* 2012;130:984–990.
50. Sobti N, Ji E, Brown RL, et al. Evaluation of acellular dermal matrix efficacy in prosthesis-based breast reconstruction. *Plast Reconstr Surg.* 2018;141:541–549.
51. Sorkin M, Qi J, Kim HM, et al. Acellular dermal matrix in immediate expander/implant breast reconstruction: a multicenter assessment of risks and benefits. *Plast Reconstr Surg.* 2017;140:1091–1100.
52. Stein MJ, Chung A, Arnaout A, et al. Complication rates of acellular dermal matrix in immediate breast reconstruction with radiation: a single-institution retrospective comparison study. *J Plast Reconstr Aesthet Surg.* 2020;73:2156–2163.
53. Vardanian AJ, Clayton JL, Roostaeian J, et al. Comparison of implant-based immediate breast reconstruction with and without acellular dermal matrix. *Plast Reconstr Surg.* 2011;128:403e–410e.
54. Weichman KE, Wilson SC, Weinstein AL, et al. The use of acellular dermal matrix in immediate two-stage tissue expander breast reconstruction. *Plast Reconstr Surg.* 2012;129:1049–1058.
55. Woo KJ, Park JW, Mun GH, et al. Does the use of acellular dermal matrix increase postoperative complications of the first-stage reconstruction of immediate expander-implant breast reconstruction: a matched cohort study. *Ann Plast Surg.* 2017;79:341–345.
56. Yoon AP, Qi J, Kim HM, et al. Patient-reported outcomes after irradiation of tissue expander versus permanent implant in breast reconstruction: a multicenter prospective study. *Plast Reconstr Surg.* 2020;145:917e–926e.
57. Davila AA, Seth AK, Wang E, et al. Human acellular dermis versus submuscular tissue expander breast reconstruction: a multivariate analysis of short-term complications. *Arch Plast Surg.* 2013;40:19–27.
58. Voineskos SH, Klassen AF, Cano SJ, et al. Giving meaning to differences in BREAST-Q scores: minimal important difference for breast reconstruction patients. *Plast Reconstr Surg.* 2020;145:11e–20e.
59. Yost KJ, Eton DT, Garcia SF, et al. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. *J Clin Epidemiol.* 2011;64:507–516.
60. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain.* 2001;94:149–158.
61. Flaherty SA. Pain measurement tools for clinical practice and research. *AANA J.* 1996;64:133–140.
62. U.S. Food and Drug Administration. Acellular dermal matrix (ADM) products used in implant-based breast reconstruction differ in complication rates: FDA safety communication. Available at https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication. Published March 31, 2021. Accessed May 18, 2021.
63. Keirns CC, Goold SD. Patient-centered care and preference-sensitive decision making. *JAMA.* 2009;302:1805–1806.
64. Lee CN, Ubel PA, Deal AM, et al. How informed is the decision about breast reconstruction after mastectomy?: a prospective, cross-sectional study. *Ann Surg.* 2016;264:1103–1109.
65. Alaofi RK, Nassif MO, Al-Hajeili MR. Prophylactic mastectomy for the prevention of breast cancer: review of the literature. *Avicenna J Med.* 2018;8:67–77.
66. Euhus DM, Diaz J. Breast cancer prevention. *Breast J.* 2015;21:76–81.
67. Morrow M, Mehrara B. Prophylactic mastectomy and the timing of breast reconstruction. *Br J Surg.* 2009;96:1–2.

68. Tuttle TM, Habermann EB, Grund EH, et al. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: A trend toward more aggressive surgical treatment. *J Clin Oncol.* 2007;25:5203–5209.
69. Wong SM, Freedman RA, Sagara Y, et al. Growing use of contralateral prophylactic mastectomy despite no improvement in long-term survival for invasive breast cancer. *Ann Surg.* 2017;265:581–589.
70. Hassanein AH, Herrera FA, Hassanein O. Challenges of randomized controlled trial design in plastic surgery. *Can J Plast Surg.* 2011;19:e28–e29.
71. American Society of Plastic Surgeons. Tracking operations and outcomes for plastic surgeons (TOPS). September 1, 2021. Available at https://www.plasticsurgery.org/for-medical-professionals/registries/tracking-operations-and-outcomes-for-plastic-surgeons?sub=Benefits+of+TOPS. Accessed November 13, 2021.