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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Acellular dermal matrix support for breast reconstruction after mastectomy [Acellulär dermal matrix för bröstrekonstruktion efter mastektomi]

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1. Abstract

Background
Long term survival after treatment for breast cancer has improved during the last decades. The need of breast reconstruction has therefore increased, both after therapeutic and prophylactic mastectomy. Immediate breast reconstruction (IBR) i.e. at the same time as the cancer surgery is increasingly often used. The surgical methods have changed towards preservation of the nipple-areola complex and skin, in an attempt to improve the final aesthetic result. To meet the demand for a proper pocket for the implant at IBR, different supporting materials like acellular dermal matrix (ADM) or synthetic matrix have been introduced.

Objective
To evaluate whether there is a difference in recurrence of cancer, major complication rates, health related quality of life (HRQoL) or aesthetic outcome when ADM (including all types) is used in immediate breast reconstruction compared to reconstruction without ADM.

Methods
A systematic literature search was conducted in in PubMed, Embase, the Cochrane Library, and a number of HTA-databases. Two authors independently screened titles, abstracts and full-text articles for inclusion and extracted data. Meta-analyses were conducted when data were possible to pool. The certainty of evidence was graded according to the GRADE system.

Main results
Twenty-eight non-randomised controlled studies and 23 case series were included in the assessment. All studies dealt with IBR after therapeutic mastectomy. The vast majority of studies had high risk of bias. No study reported on recurrence of cancer or HRQoL.
Implant loss
The pooled risk ratio (RR) was 1.05 (95% confidence interval (CI) 0.71; 1.5) for ADM versus no ADM, based on 16 studies. Four studies reported implant loss per patient RR 1.33 (95% CI 0.73; 2.43). Very low certainty of evidence (GRADE ⊕◯◯◯).
Infection
The pooled RR was 1.55 (95% CI 1.17; 2.05) for ADM versus no ADM, based on 16 studies. Five studies reported infection per patient; RR 1.31 (95% CI 1.15; 1.49). Very low certainty of evidence (GRADE ⊕◯◯◯).
Complications
The pooled RR was 1.27 (95% CI 0.95; 1.69) comparing ADM with no ADM, based on 17 studies. Five studies reported total complications per patient; RR 1.07 (95% CI 0.95; 1.21). Low certainty of evidence (GRADE ⊕⊕◯◯).
Aesthetic result
Three studies evaluated the aesthetic outcome in 635 breasts. They used different and non-validated scales and the reported results were inconsistent. Very low certainty of evidence (GRADE ⊕◯◯◯).
Capsular contraction
The pooled RR was 0.80 (95% CI 0.38; 1.69) comparing ADM with no ADM, based on five studies. Very low certainty of evidence (GRADE ⊕◯◯◯).

Concluding remark
Despite a large number of studies of immediate breast reconstruction after mastectomy in women at risk or with breast cancer, the certainty of evidence is low or very low for efficacy and safety of acellular dermal matrix. There are no studies on recurrence of cancer or HRQoL. Randomised controlled trials are urgently needed.

2. Svensk sammanfattning – Swedish summary

Bakgrund

Överlevnaden efter behandling av bröstcancer har förbättrats under de senaste decennierna. Behovet av bröstrekonstruktion har därför ökat, både efter terapeutisk och efter profylaktisk mastektomi. Bröstrekonstruktion i direkt anslutning till canceroperationen har blivit allt vanligare. För att förbättra det kosmetiska resultatet sparas allt oftare bröstvårta och vårtgård. Sedan mitten på 2000-talet används ofta så kallade acellulära dermala matrix (ADM) vid bröstrekonstruktioner. De kan utvinnas från t.ex. hud eller hjärtsäck. I en speciell process tas då alla celler och antigener bort, varefter matrixen sys in som invändigt stöd för en protes. På senare år har också icke-biologiska material börjat användas i samma syfte.

Syfte

Att studera om användandet av ADM (inkluderande alla typer), jämfört med att inte använda ADM vid direkt bröstrekonstruktion innebär en ökad risk avseende onkologisk säkerhet och komplikationer, samt om hälsorelaterad livskvalitet och estetiskt resultat påverkas.

Metoder

Under maj 2016 gjordes systematiska litteratursökningar i PubMed, Embase, the Cochrane Library, Cinahl, och flera HTA-databaser. Minst två författare granskade titlar, abstracts och fulltextartiklar, värderade studiekvalitet och extraherade data oberoende av varandra. Det vetenskapliga underlagets styrka bedömdes enligt GRADE-systemet.

Resultat

Tjugoåtta icke-randomiserade, kontrollerade studier och 23 fallserier inkluderades i rapporten. Ingen studie redovisade resultat efter enbart profylaktisk mastektomi. Majoriteten av studierna hade allvarliga studiebegränsningar. Ingen studie rapporterade onkologiska utfall eller effekter avseende hälsorelaterad livskvalitet.

Protesförlust:

I en meta-analys av 16 kohortstudier var den relativa risken (RR) för protesförlust, analyserat per bröst, 1,05 (95% konfidensintervall (KI) 0,71; 1,5) för rekonstruktion med ADM jämfört med utan ADM. Vid analys per patient var RR 1,33 (95% KI 0,73; 2,43).

Otillräckligt vetenskapligt underlag (GRADE ⊕◯◯◯).

Infektion:

I en meta-analys av 16 kohortstudier var RR, analyserat per bröst, 1,55 (95% KI 1,17; 2,05) för ADM jämfört med icke-ADM. Vid analys per patient var RR 1,31 (95% KI 1.15; 1.49).

Otillräckligt vetenskapligt underlag (GRADE ⊕◯◯◯).

Komplikationer:

I en meta-analys av 17 kohortstudier var RR, analyserat per bröst, 1,27 (95% KI 0.95; 1.69) för ADM jämfört med icke-ADM. Vid analys per patient var RR 1,07 (95% KI 0,95; 1,21).

Begränsat vetenskapligt underlag (GRADE ⊕⊕◯◯).

Estetiskt resultat:

Tre studier rapporterade estetiskt utfall för sammanlagt 635 bröst. Olika icke-validerade skalor användes och resultaten i de olika studierna var motstridiga.

Otillräckligt vetenskapligt underlag (GRADE ⊕◯◯◯).

Kapselkontraktur:

I en meta-analys av fem kohortstudier var RR, analyserat per bröst, 0,80 (95% KI 0,38; 1,69) för ADM jämfört med icke-ADM. Otillräckligt vetenskapligt underlag (GRADE ⊕◯◯◯).

Sammanfattande bedömning

Trots att ett stort antal studier har gjorts med ADM vid direkt bröstrekonstruktion i anslutning till mastektomi på kvinnor med hereditärt förhöjd risk eller med bröstcancer saknas det helt studier som belyser den onkologiska säkerheten. Resultaten som indikerar en ökad risk för infektion är osäkra p.g.a. allvarliga studiebegränsningar. Det vetenskapliga underlaget är otillräckligt avseende specifika komplikationer och estetiskt resultat. Randomiserade studier är angelägna.

The above summaries were written by representatives from the HTA-centrum. The HTA-report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers, and is ended with a concluding summary.

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3. Summary of Findings

The use of acellular dermal matrix (ADM, all types) vs. no ADM for breast reconstruction after mastectomy.

Outcome variable	Study design Number of studies	Relative effect (95%CI)	Absolute effect (crude numbers)	Certainty of evidence GRADE[1]
Mortality	0	-	-	
Recurrence of cancer	0	-	-	
Implant loss (per breast)	Cohort studies (16)	1.05 (0.71; 1.56)	4.0% vs 1.9%	⊕◯◯◯ Very low[1]
Implant loss (per patient)	Cohort studies (5)	1.33 (0.73; 2.43)	9.8% vs 3.5%	
Infection (per breast)	Cohort studies (16)	1.55 (1.17; 2.05)	6.4% vs 3.5%	⊕◯◯◯ Very low[2]
Infection (per patient)	Cohort studies (5)	1.31 (1.15; 1.49)	3.9% vs 3.0%	
Total complications (per breast)	Cohort studies (12)	1.27 (0.95; 1.69)	21.3% vs 14.6%	⊕⊕◯◯ Low[3]
Total complications (per patient)	Cohort studies (5)	1.07 (0.95; 1.21)	5.8% vs 5.1%	
Aesthetic outcome	Cohort studies (3)	-	Inconsistent results	⊕◯◯◯ Very low[1]
Capsular contraction	Cohort studies (5)	0.80 (0.38; 1.69)	5.6% vs 9.6%	⊕◯◯◯ Very low[4]

Footnotes:
[1] Downgrade due to serious study limitations and inconsistency.
[2] Downgrade due to serious study limitations.
[3] Some study limitations but not enough to downgrade (per patient data).
[4] Downgrade due to serious study limitations and inconsistency.

Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

ADM	Acellular dermal matrix
DBR	Delayed breast reconstruction
HRQoL	Health Related Quality of Life
IBR	Immediate breast reconstruction
RCT	Randomised controlled trial
RT	Radiotherapy
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SU	Sahlgrenska University Hospital
VGR	Region Västra Götaland

5. Background

Breast Cancer

The long term survival of breast cancer has improved due to improved multimodal therapies during the last decades. The five-year survival rate in Region Västra Götaland (VGR) was 87 % during 2006-2010, which is in accordance with national Swedish data (Regionalt cancercentrum 2015).

There are subgroups of women who either have a known gene mutation associated with a 50 - 80 % lifetime risk to develop breast cancer, or an unknown hereditary condition with a higher than 20 % risk to develop breast cancer. These high risk patients either undergo an annual x-ray for early detection of malignancy in the breast, or prophylactic surgery with complete removal of the breast tissue. It has been shown that prophylactic surgery substantially reduces the incidence of breast cancer in this group of women. However, surgery is associated with risk for complications (Arver et al., 2011)

A consequence of the improved prognosis after therapeutic or prophylactic surgery is an increased need of breast reconstruction.

Prevalence and incidence

About one out of ten of all Swedish women will be diagnosed with breast cancer during her life. It is estimated that about 400 - 500 women in Region Västra Götaland have a gene mutation, and an additional 1,600 women have an increased risk of developing breast cancer.

Breast reconstruction surgery

The aim of breast reconstruction after therapeutic or prophylactic surgery is to restore symmetry and to achieve a good aesthetic result. Although breast reconstruction *per se* probably is not the main determining factor for health related quality of life (HRQoL) after breast cancer surgery (Harcourt 2001), a successful reconstruction can help to improve HRQoL (Kim et al., 2015).

Different breast reconstructive surgical procedures have been described. In patients who have received radiotherapy, which has been shown to increase the risk of complications (Kronowitz et al., 2009), breast reconstructions are usually performed using autologous tissue (latissimus dorsi flap, or deep inferior epigastric perforator flap). In non-irradiated patients reconstruction is generally performed with either an expander implant or a permanent implant, sometimes combined with a local flap.

Due to various reasons, such as the characteristics of the tumour, planned radiotherapy or other factors, the reconstruction is often performed some time after the primary cancer surgery. This is called, *delayed breast reconstruction* (DBR). During latter years, the number of referrals for an *immediate breast reconstruction* (IBR), i.e. to perform the reconstruction during the same operative procedure as the cancer surgery, has increased. This is the case for patients with a diagnosed breast cancer, as well as for women with an increased risk (heredity) for breast cancer.

During recent years, there has been a change in the surgical technique of immediate reconstructions. New knowledge with regard to the safety margins of excision, and the low risk to develop breast cancer in nipple-sparing mastectomy, are now taken into consideration. Today, the surgeon will attempt to preserve the nipple-areola complex and skin in order to improve the final aesthetic result, and, thereby, also to improve the patients well-being and HRQoL. This increases the demand for a proper pocket for the implant that can either be an expanded implant (that will be changed later) or a permanent implant. The traditional way to achieve this pocket is to raise the major pectoral muscle in

combination with the serratus muscle to cover the upper-lateral part of the implant. However, in doing so the lower part of the breast will only be covered by the remaining thin skin.

The IBR can be performed as a one-stage operation when a permanent implant is placed in the pocket, as described above. It can also be performed as a two-stage procedure when an expander implant is placed in the pocket at the first operation. After a various number of fillings, the expander implant is finally replaced with a permanent implant in a later operation.

The normal pathway through the health care system and current wait time for medical assessment and treatment

Breast reconstruction surgery in VGR is predominantly performed at the Department of Reconstructive Plastic Surgery, Sahlgrenska University Hospital. Most reconstructions are performed as delayed procedures, with a total of about 150 - 200 operations annually.

Women with a known gene mutation, i.e. with a higher risk than that of the normal population, or with a diagnosed breast cancer who request an IBR are referred to the Department of Reconstructive Plastic Surgery from either the Department of Oncology at the hospital, or from a breast cancer unit in the region. These patients are discussed at a multidisciplinary meeting with specialists in plastic surgery, breast surgery, oncology, and oncogenetics. Since it has been reported that there is an increased risk of early and late complications associated with radiotherapy in patients who have IBR we currently have a conservative approach to perform IBR if radiotherapy is planned.

Number of patients per year who undergo immediate breast reconstruction

About 40 - 50 women with familiarly increased risk of breast cancer, and 40 -50 patients with diagnosed cancer undergo an IBR each year at the Department of Reconstructive Plastic Surgery. It is expected that this number will increase.

Present recommendations from medical societies or health authorities

Today, there is no international or national consensus regarding when, and how, to perform an IBR. Different clinics in Sweden use various approaches as to spare the nipple-areola complex, to use acellular dermal matrix (ADM), to do the reconstruction in one or two stages, or to do an IBR when irradiation is planned.

6. Acellular dermal matrix in immediate breast reconstruction

In 2005 a novel method to cover the lower part of the breast was introduced. This could be done by a novel type of matrix prepared from the skin of a pig or from a human cadaver. All cells and antigens are removed from the skin tissue, which leaves an acellular dermal matrix (ADM). This matrix could then be sutured to the distal part of the major pectoral muscle and to the sub-mammary fold creating an 'internal bra'. Several different types of ADM from different tissues and species, for instance ADM from the calf pericardium or from the porcine intestinal mucosa, are available. Some non-biological synthetic matrices have also been introduced. Acellular dermal matrix from human cadaver is not allowed in Sweden. In practice and in this report, ADM refers to all types of matrices.

A number of advantages using ADM in IBR have been postulated. These include reduction of postoperative pain, fewer expansions or even an eliminated need for expanders, shorter operative time, less capsular modifications at the stage II surgery, decreased incidence of capsular contractions, decreased rate of revisions, and improved aesthetic outcome.

At the Department of Reconstructive Plastic Surgery, Sahlgrenska University Hospital, we have the experience of using ADM in IBR since 2007. Initially only a matrix prepared from porcine intestinal mucosa, Surgisis®, was used. Since 2014 also the biologic matrix made of calf pericardium, Veritas®, and the non-biologic matrix TIGR® have been used.

7. Objective

Question at issue:
Is there a difference in recurrence of cancer, major complication rates, health related quality of life, aesthetic outcome, or risk to develop capsular contraction when ADM (any type) is used in breast reconstruction compared to a reconstruction without the use of a matrix?

P	Women who undergo immediate breast reconstruction after subcutaneous mastectomies due to breast cancer, in situ breast cancer, a high risk of breast cancer or due to a proven breast cancer genome Subgroup: Radiation therapy or not Subgroup: Reconstruction in one or two stage(s)
I1	ADM (Acellular dermal matrix); Biological matrix ~~Subgroup: species~~
I2	ADM; Synthetic mesh/matrix
C	No matrix/mesh
O	Critical for decision making Recurrence of cancer HRQoL (Health Related Quality of Life) Major complications i.e. Implant loss, Infections Complications (including implant loss, infections, capsular contraction and other) Aesthetic result Important for decision making Capsular contraction Delay of adjuvant treatment due to breast reconstruction complications Not important for decision making -

8. Methods

Systematic literature search

During May 2016 two authors (TS, IS) performed systematic searches in PubMed, Embase, the Cochrane Library, the CRD database and the websites of the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) and the Norwegian Knowledge Centre for the Health Services. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts, and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the participants of the project group. All authors read the articles independently of one another, and it was finally decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

The included studies, their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The included studies have been critically appraised using a checklist for assessment of cohort studies, modified from SBU by HTA-centrum. The results and the assessed quality of each article have been summarised per outcome in Appendices 4:1 – 4:5. Data were extracted by at least two authors per outcome. When possible, data were pooled in meta-analyses using RevMan 5.2 and presented as forest plots. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 7). The certainty of evidence was defined according to the GRADE system (Atkins et al., 2004; GRADE Working Group).

Ongoing research

A search was performed in Clinicaltrials.gov 2016-09-29 using the search terms (strattice OR veritas OR alloderm OR tigr OR surgisis OR permacol OR dermamatrix OR neoform OR FlexHD OR Allomax OR Surgimed OR Vicryl OR seri OR "acellular dermal matrix" OR "acellular dermal matrices") AND (breast OR Mastectomy OR Mammaplasty OR Mastectomies OR Mammaplasties).

9. Results

Literature search (Appendix 1)

The literature search identified 629 articles after removal of duplicates. After reading the abstracts 501 articles were excluded. Another 30 articles were excluded by two authors (TS, IS) after reading the articles in full text. The remaining 98 articles were sent to all participants of the project group, and 51 articles (28 non-randomised controlled studies and 23 case series) were finally included in the assessment (Appendix 2). All studies included patients with breast cancer. Few cases of breast reconstruction after prophylactic mastectomy were included and none of these were reported separately.

Critical outcomes for decision making

Recurrence of cancer

No study reported data on recurrence of cancer.

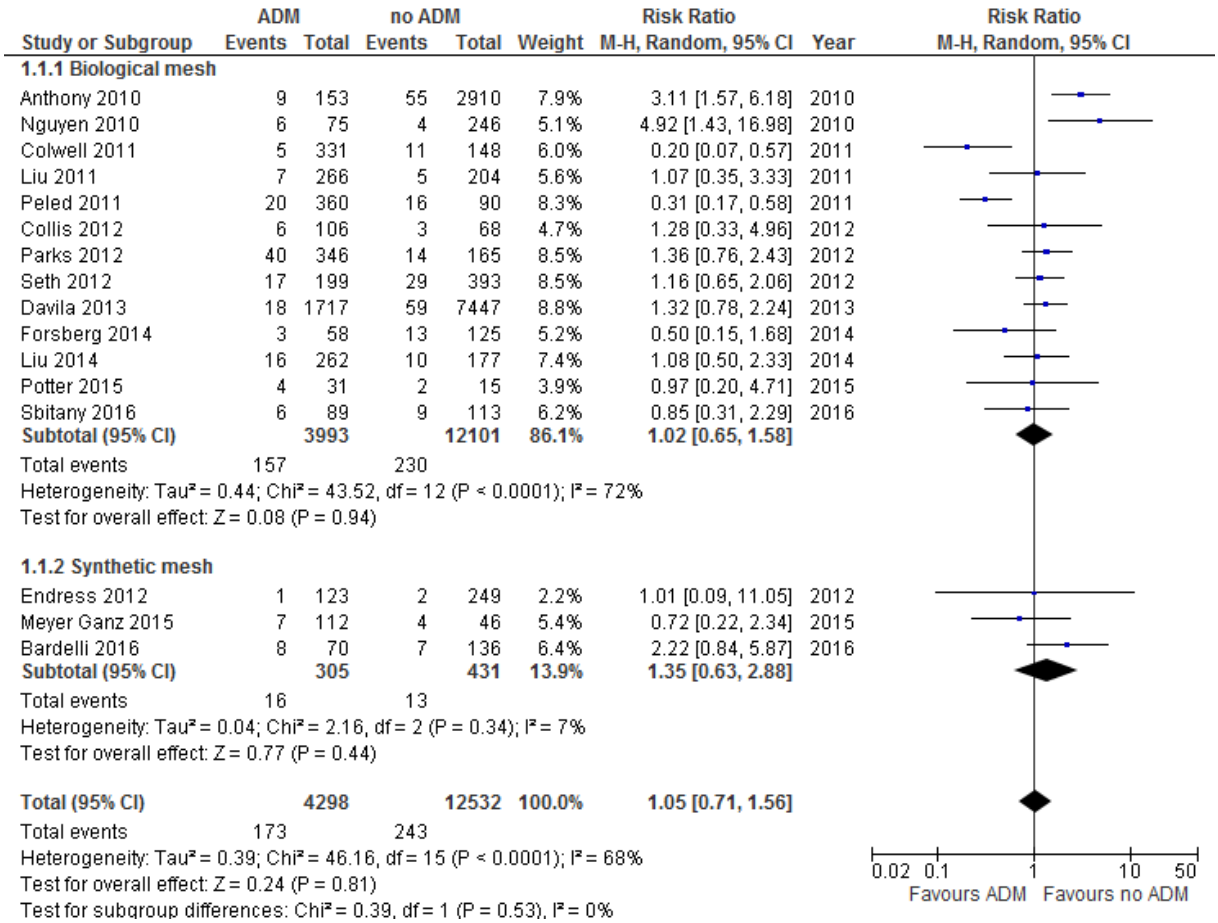
HRQoL (Health Related Quality of Life)

No study reported data on health related quality of life.

Implant loss (Appendix 4.1)

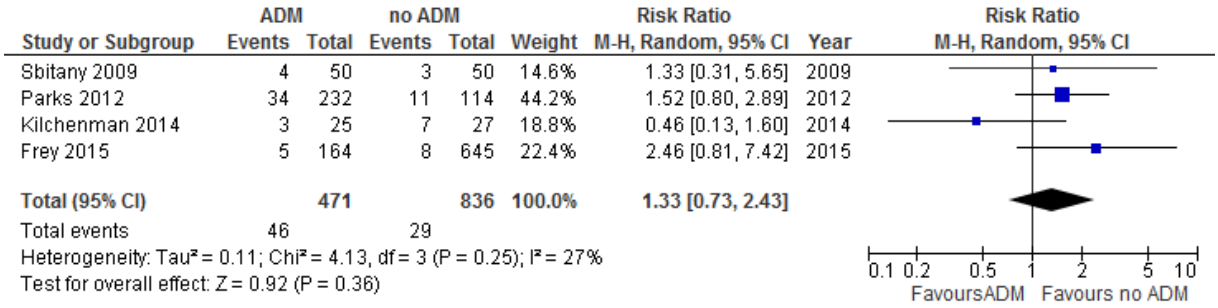
Sixteen cohort studies and 21 case series reported the incidence of implant loss per breast. All the cohort studies had severe study limitations. A meta-analysis of studies that used biological mesh (ADM) demonstrated a high heterogeneity between the studies. The pooled relative risk ratio was 1.02 with a 95% confidence interval of 0.65 to 1.58, including 16,830 breasts (Figure 1). A meta-analysis of studies that used synthetic meshes did not reveal a significant difference between the study groups.

Figure 1. Meta-analysis of studies comparing ADM vs no ADM.
Unit of analysis: Breast.
Outcome: Implant loss.



Four studies reported implant loss per patient. Also these studies had severe study limitations. The pooled relative risk ratio was 1.33 with a 95 % confidence interval of 0.73 to 2.43, including 1,307 patients (Figure 2). None of the studies that used synthetic mesh reported data per patient.

Figure 2. Meta-analysis of studies comparing ADM vs no ADM.
Unit of analysis: Patient.
Outcome: Implant loss.

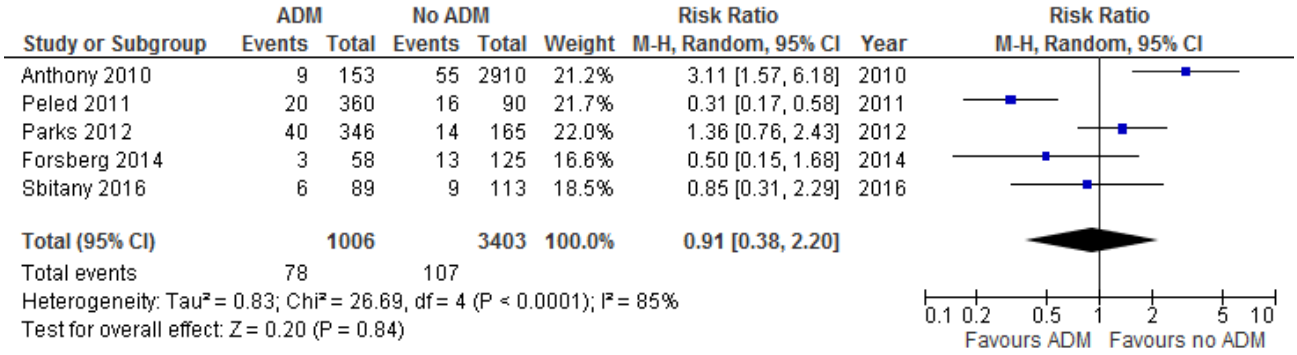


The case series reported implant loss at frequencies varying from 0-17 % (Appendix 4.1).

Pre-specified subgroup evaluation: radiotherapy
No study reported results in subgroups according to radiotherapy. All studies included patients with pre-or post-operative radiotherapy or both (Appendix 4.1). No formal analysis could be conducted. By adding the distribution of radiotherapy to each study in the meta-analyses (Fig.1-2), no obvious sign of impact on the rate of implant loss following radiotherapy could be detected.

Pre-specified subgroup evaluation: one-and two-stage procedure
Among the 16 cohort studies, eight had used two-stage procedures and the remaining studies had mixed populations and did not report one- and two-stage procedures separately. In a subgroup analysis of five studies applying biological mesh in two stage-procedures, the heterogeneity was high. The pooled relative risk ratio was 0.91 with a 95% confidence interval of 0.38 to 2.20 (Figure 3).

Figure 3. Meta-analysis of studies comparing ADM vs no ADM (subgroup two-stage procedures)
Unit of analysis: Breast.
Outcome: Implant loss.

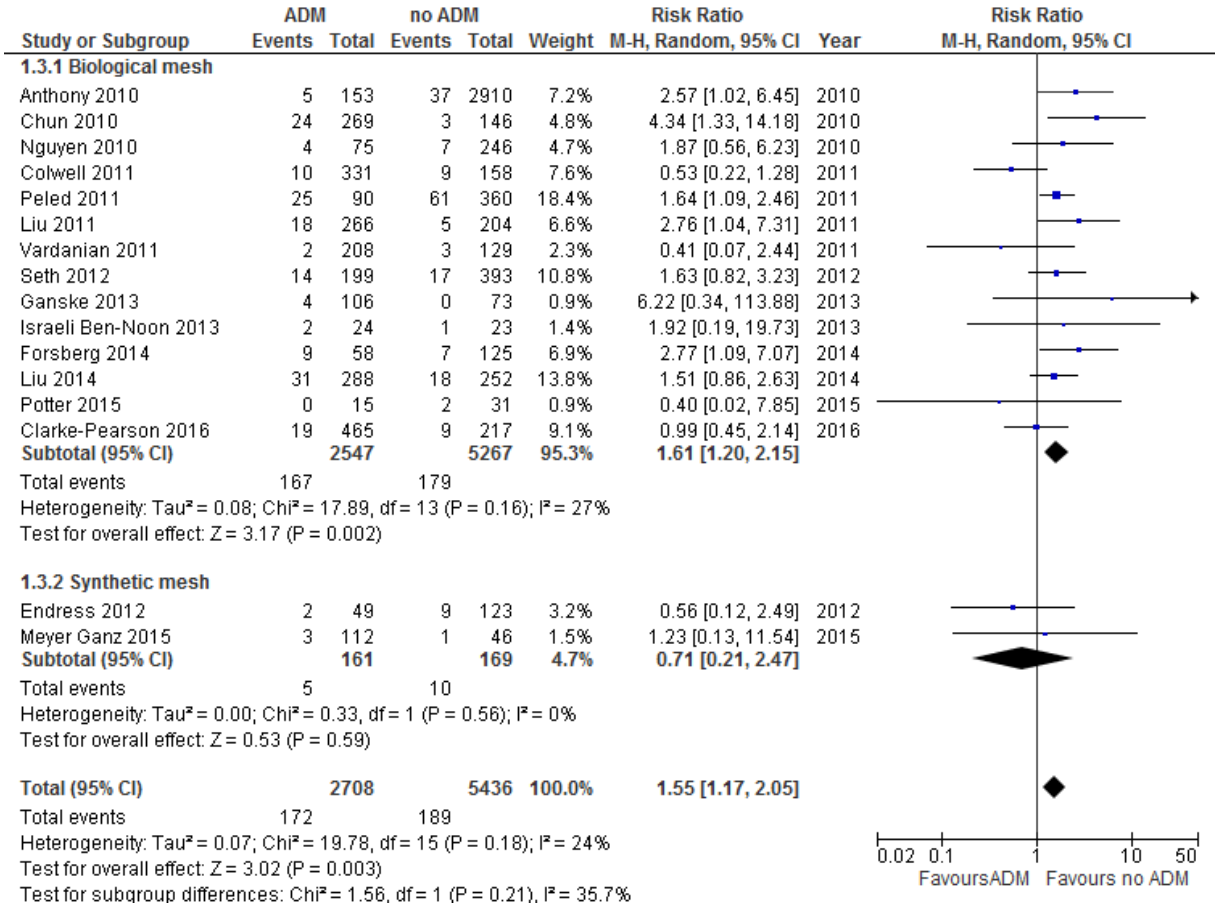


Conclusion: It is uncertain whether there is little or no difference in the incidence of implant loss after breast reconstruction with ADM compared with no ADM in women with surgery for breast cancer. Very low certainty of evidence (GRADE ⊕◯◯◯).

Infections (Appendix 4.2)

Twenty-one cohort studies and 20 case series reported the incidence of infection. All the cohort studies had severe study limitations. A meta-analysis of studies that used biological mesh (ADM), including 8144 breasts, demonstrated an increased risk of infection with a relative risk ratio of 1.61 and a 95 % confidence interval of 1.20 to 2.15 (Figure 4). A meta-analysis of studies that used synthetic meshes compared with no mesh, revealed no significant difference between the study groups.

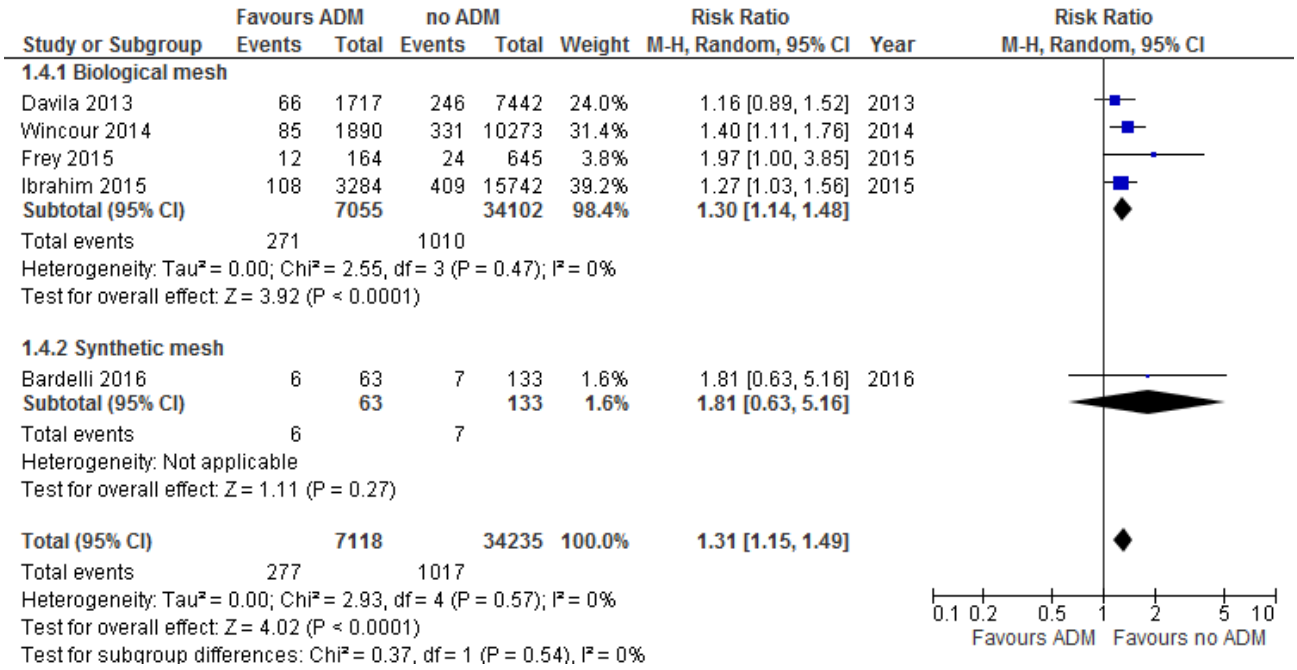
Figure 4. Meta-analysis of studies comparing ADM vs no ADM.
Unit of analysis: Breast.
Outcome: Infection.



The case series reported the rate of infection varying between 0 - 17 % (Appendix 4.2).

Five studies reported results per patient (Figure 5). The pooled relative risk ratio was 1.30 with a 95 % confidence interval of 1.14 to 1.48 for the four studies using biological mesh compared with no mesh.

Figure 5. Meta-analysis of studies comparing ADM vs no ADM.
Unit of analysis: Patient.
Outcome: Infection.



<u>Conclusion:</u> It is uncertain whether the use of ADM in breast reconstruction increases the risk of infection compared with not using ADM in women operated for breast cancer.
Very low certainty of evidence (GRADE ⊕◯◯◯).

Complications (Appendix 4.3)

Seventeen cohort studies and 18 case series reported the total incidence of complications. All the cohort studies had severe study limitations. A meta-analysis demonstrated a high heterogeneity. The pooled relative risk ratio for the ten studies using biological mesh compared with no mesh, including 6,122 breasts, was 1.31 with a 95 % confidence limit of 0.94 to 1.81 (Figure 6). Five studies reported results per patient (Figure 7).

Fig. 6. Meta-analysis of studies comparing ADM vs no ADM.
Unit of analysis: Breast.
Outcome: Complications.

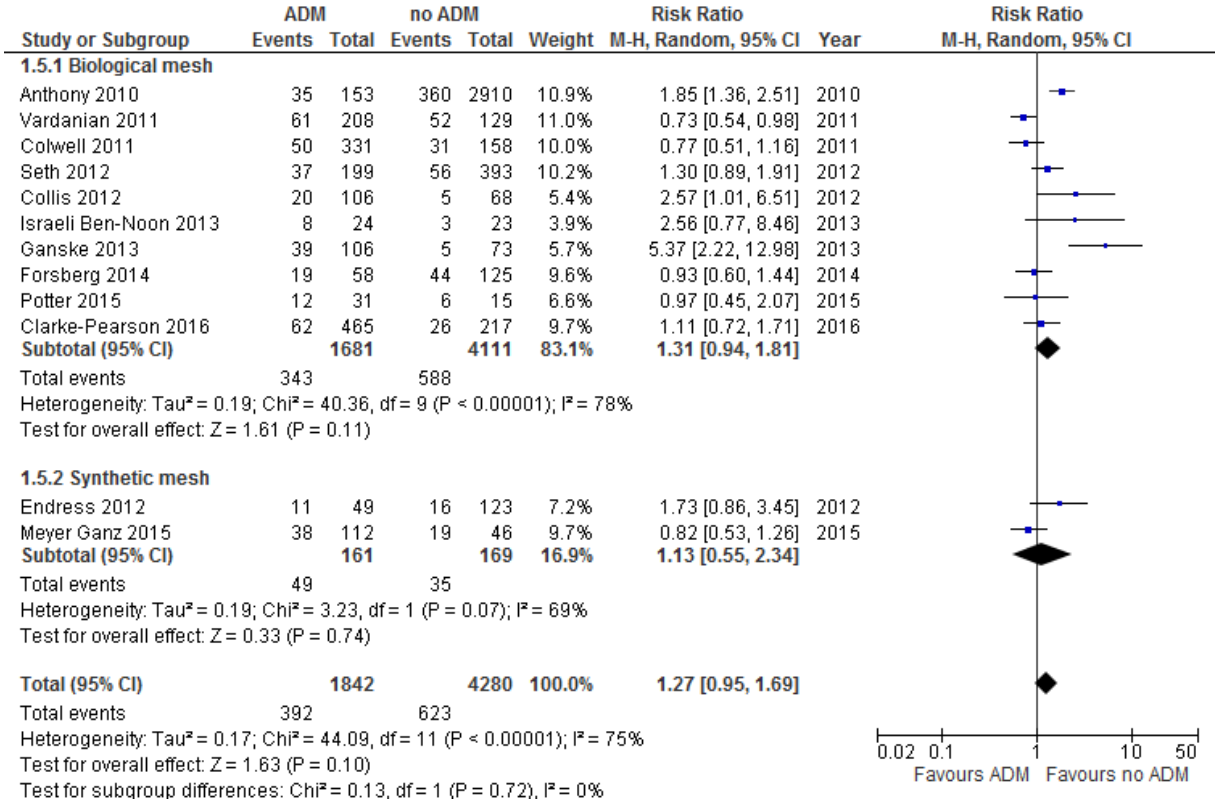
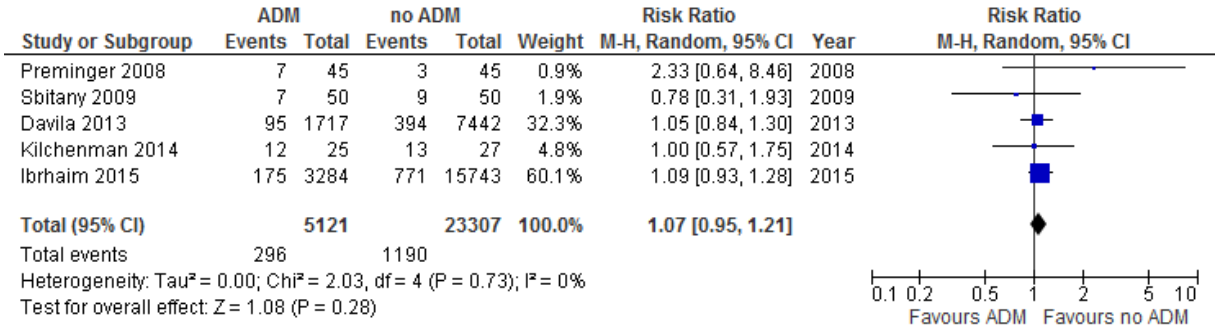


Fig. 7. Meta-analysis of studies comparing ADM vs no ADM (biological mesh).
Unit of analysis: Patient.
Outcome: Complications.



The case series reported rates of complications varying between 4 - 41 % (Appendix 4.3).

Conclusion: The use of ADM in breast reconstruction may result in little or no difference in the rate of complications compared without the use of ADM in women operated for breast cancer.
Low certainty of evidence (GRADE ⊕⊕◯◯).

Aesthetic outcome (Appendix 4.4)

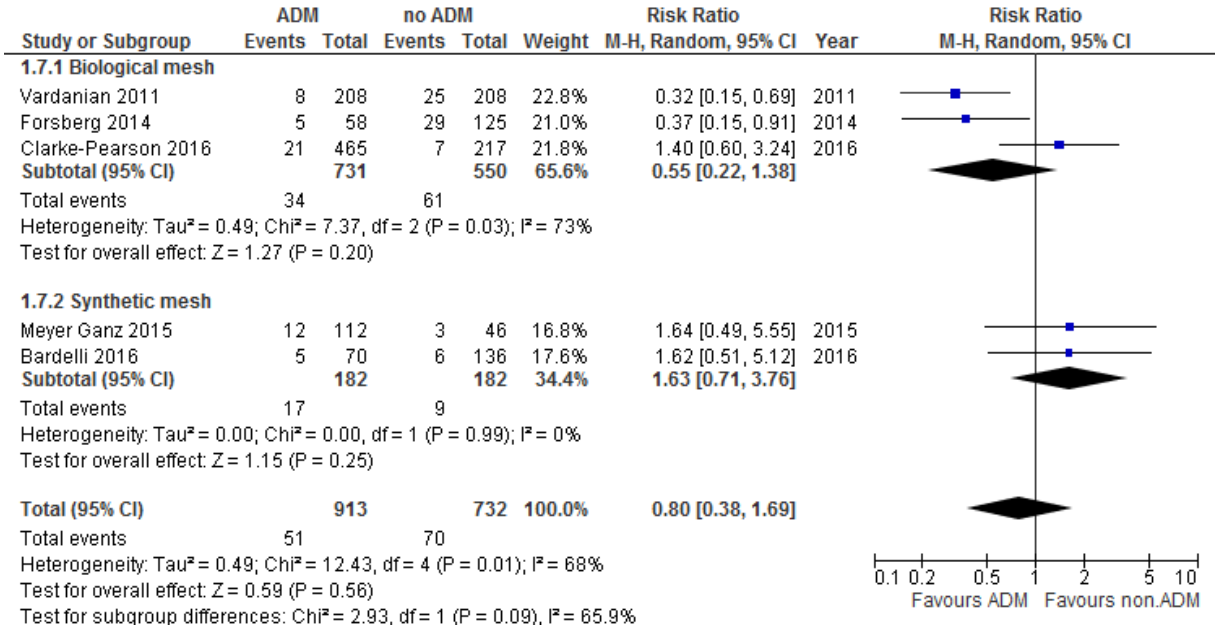
Only three studies have evaluated the aesthetic outcome after breast reconstruction. A total of 328 breasts were reconstructed with ADM, and 307 breasts were reconstructed without ADM. The aesthetic results were scored by evaluators who were unaware of the surgical method. None of the studies reported how the women themselves judged the final aesthetic result.
Two studies reported different results with regard to the overall aesthetic outcome. A statistically significant improved aesthetic score was reported in one, while the opposite was reported in the other study. The third study only reported five different sub-scores with no consistent results in favour of either of the two methods. None of studies used validated scales.
Conclusion: It is uncertain whether there is little or no difference in aesthetic outcome following the use of ADM in patients with surgery for breast cancer.
Very low certainty of evidence (GRADE ⊕◯◯◯).

Outcomes important for decision making

Capsular contraction (Appendix 4.5)

Five cohort studies and five case series reported the incidence of capsular contraction. All the cohort studies had severe study limitations. A meta-analysis demonstrated moderate heterogeneity. The pooled relative risk ratio using biological mesh compared with no mesh, including 1645 breasts, was 0.55 with a 95 % confidence interval of 0.38 to 1.69 (Figure 8).

Figure 8. Meta-analysis of studies comparing ADM vs no ADM.
Unit of analysis: Breast.
Outcome: Capsular contraction.



The case series reported capsular contraction at various frequencies; 0.4 - 13 % (Appendix 4.5).

Conclusion: It is uncertain whether there is little or no difference in the incidence of capsular contraction after breast reconstruction with ADM compared with no ADM in women operated for breast cancer. Very low certainty of evidence (GRADE ⊕◯◯◯).

Postponement of adjuvant treatment
In one case series (Barber et al. 2015), it was reported that 7 of 27 (26 %) of the patients who required adjuvant therapy had this delayed due to problems with the reconstruction.

10. Ethical issues

The aesthetic outcome when ADM is used in breast reconstruction surgery is poorly documented. It is also unclear whether complication rate increases with the use of ADM. Presently it can merely be speculated that the use of ADM may improve aesthetic outcome, but this may be at the price of increased complications. Thus, it is difficult for the patient to make an informed decision on type of breast reconstruction.

11. Organisational aspects

Time frame for the introduction of acellular dermal matrix in breast reconstruction
Acellular dermal matrix is already used both nationally and internationally. At Sahlgrenska University Hospital ADM it is currently used only in an ongoing prospective randomised trial (‘Västsvenska ADM studien’). The outcome from this, and other ongoing trials, will serve as guidance whether the technique should be introduced as a clinical routine procedure.

Present use of acellular dermal matrix in other hospitals in Region Västra Götaland
To our knowledge ADM is not used in other hospitals in VGR.

Consequences of the use of acellular dermal matrix for personnel
If ADM are introduced in the clinical routine for primary use in breast reconstructions there will be a need for education, as well as training how to use this material.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland
No obvious consequences.

12. Economic aspects

Present costs of breast reconstruction without acellular dermal matrix

The cost of one IBR procedure is estimated to be 117,000 SEK. This includes the cost for hospital stay, but excludes additional costs for out-patients clinic visits.

Expected costs of breast reconstruction with acellular dermal matrix

The extra cost to use ADM for the reconstruction of one breast ranges from 6,000 SEK for the synthetic meshes to 25,000 SEK for the biological meshes.

Total change of cost

The cost to perform IBR will increase with use of ADM. However, provided that the aesthetic outcome is improved when ADM is used the need for further corrections may be reduced, and thereby the net total cost may decrease. If complications will be more frequent using ADM, the total costs for out-patient clinic visits and reoperations will increase. Thus, it is not possible at the present time to make a proper estimation whether the use of ADM will increase or decrease the total net cost of successful breast reconstructions.

Possibility to adopt and use acellular dermal matrix within the present budget

Currently there is no funding for the extra costs to use ADM in IBR.

Available economic evaluations or cost advantages/disadvantages

Only a few studies have tried to analyse the economical aspect of an increased use of ADM (Krishnan et al., 2013, Krishnan et al., 2014, Bank et al., 2013, De Blacam et al., 2012). However, all are of poor scientific quality, and are thus inconclusive.

13. Discussion

Summary of main results

The introduction of ADM has changed the technique of implant based breast reconstruction. Several advantages have been suggested and it has therefore been widely used during the last 10 to 15 years. However, the scientific documentation of its superiority compared to other surgical techniques has been questioned.

The main goal for breast cancer and prophylactic breast surgery is respectively, to reduce the risk of recurrence and to prevent future cancer. Data on these outcome variables are needed for different surgical reconstruction techniques. However, no controlled study has addressed these important issues. One aim of breast reconstruction is to increase the HRQoL. No study has reported this outcome.

In this systematic review we have found that the quality of published studies is very low. The results of the present HTA and meta-analyses are uncertain, but suggest that the use of ADM is associated with an increased risk of infection.
The ultimate complication of a breast reconstruction is an implant loss, i.e. the implant has to be removed due to one or more complications. The meta-analyses did not support an association between ADM and implant loss, but they have to be interpreted with caution, since all studies had severe limitations. Furthermore, there was no indication that the use of ADM is associated with an increased risk for complications.

One of the postulated advantages using ADM has been that it may reduce the incidence of capsular contraction. Long-term follow-up is needed to confirm this. Only five studies, three with biological and two with synthetic mesh, have reported on this matter. The results of these studies are inconsistent, and the meta-analysis has to be interpreted with caution.

Radiation therapy is an important factor that may influence the result of breast surgery in both short and long term, increasing the risk for complications. Unfortunately, no study has reported the complication rates associated with radiotherapy separately for women who have had breast reconstruction with ADM compared with those in whom ADM have not been used. Thus, a proper subgroup analysis could not be performed.

It is difficult to evaluate the aesthetic result after breast reconstruction. No validated instruments are available. In this review we only found three studies that tried to evaluate the aesthetic outcome. They used different methods and their results were inconsistent with one another.

Only one case series have reported that one out of four patients who required adjuvant therapy had this treatment delayed due to problems with the surgical reconstruction. However, if this had any impact on the prognosis is unknown.

The results of all reported outcome variables had very low or low certainty of evidence. Thus, the clinical applicability of these study results is very limited, and the need for further research is evident.

14. Future perspective

Scientific knowledge gaps

There is still a lack of high quality studies that compare the use of ADM with no ADM in IBR. Randomised controlled trials are needed. Moreover, controlled trials that further analyse the impact of radiotherapy, type of ADM, and type of procedure (one-or two stage) are necessary. In these studies survival, other oncological outcome variables, health related quality of life, aesthetic outcome, and complications need to be addressed.

Ongoing research (Appendix 5)

The search in Clinicaltrials.gov 2016-09-29 identified 42 trials. Eleven of them are RCTs that are relevant for the question at issue. Two studies compare the use of ADM versus the use of a serratus pocket (NCT00616824 and NCT00692692). Both studies have been completed but no data is yet available. Four studies are designed to compare biological versus non biological meshes (NCT02830685, NCT02831426, NCT0256270 and NCT02985073). One has been completed but has not reported its results. One is still recruiting patients, and two have not started to recruit patients. Four studies are designed to compare different ADMs (NCT02521623, NCT02891759, NCT01310075 and NCT02372305). Two of them have started to recruit patients and two have not.

Ongoing research at the Department of Plastic and Reconstructive Surgery, Sahlgrenska university Hospital

A randomised controlled trial that compares a biological mesh (Veritas®) versus a synthetic mesh (TIGR®) in IBR (NCT02985073) is ongoing and recruiting.

15. Participants in the project

The question was nominated by
Anna Elander, Head of the Department of Reconstructive Plastic Surgery, Sahlgrenska University Hospital, Göteborg, Sweden.

Participating health care professionals
Håkan Hallberg, M.D.
Richard Lewin, M.D., Ph.D.
Gennaro Selvaggi, M.D., Ph.D.
all from Department of Reconstructive Plastic Surgery, Sahlgrenska University Hospital, Göteborg, Sweden.
Svanheidur Rafnsdottir, MD, Department of General Surgery, Sahlgrenska University Hospital, Göteborg, Sweden.

Participants from the HTA-centrum
Ola Samuelsson, M.D., Associate professor
Annika Strandell, M.D., Associate professor
Ida Stadig, Librarian
Therese Svanberg, HTA-librarian

External reviewer
Olle Nelzén, MD, Associate professor, Department of Surgery, Skaraborg Hospital, Skövde, Sweden.
Ulla Wide Boman, Associate professor, licensed psychologist,
Public Dental Service, Region Västra Götaland, Gothenburg Sweden

Declaration of interest
No one of the authors has any conflict of interest to declare.

Project time
HTA was accomplished during the period of 2016-05-01 – 2017-01-25. The literature searches were made in May 2016.

Appendix 1, Search strategy, study selection and references

Question at issue:

Is there a difference in recurrence of cancer, major complication rates, health related quality of life, aesthetic outcome, or risk to develop capsular contraction when ADM (any type) is used in breast reconstruction compared to a reconstruction without the use of a matrix?

P	Women who undergo immediate breast reconstruction after subcutaneous mastectomies due to breast cancer, in situ breast cancer, a high risk of breast cancer or due to a proven breast cancer genome Subgroup: Radiation therapy or not Subgroup: Reconstruction in one or two stage(s)
I1	ADM (Acellular dermal matrix); Biological matrix ~~Subgroup: species~~
I2	ADM; Synthetic mesh/matrix
C	No matrix/mesh
O	<u>Critical for decision making</u> Recurrence of cancer HRQoL (Health Related Quality of Life) Major complications i.e. Implant loss, Infections Complications (including implant loss, infections, capsular contraction and other) Aesthetic result <u>Important for decision making</u> Capsular contraction Delay of adjuvant treatment due to breast reconstruction complications <u>Not important for decision making</u> -

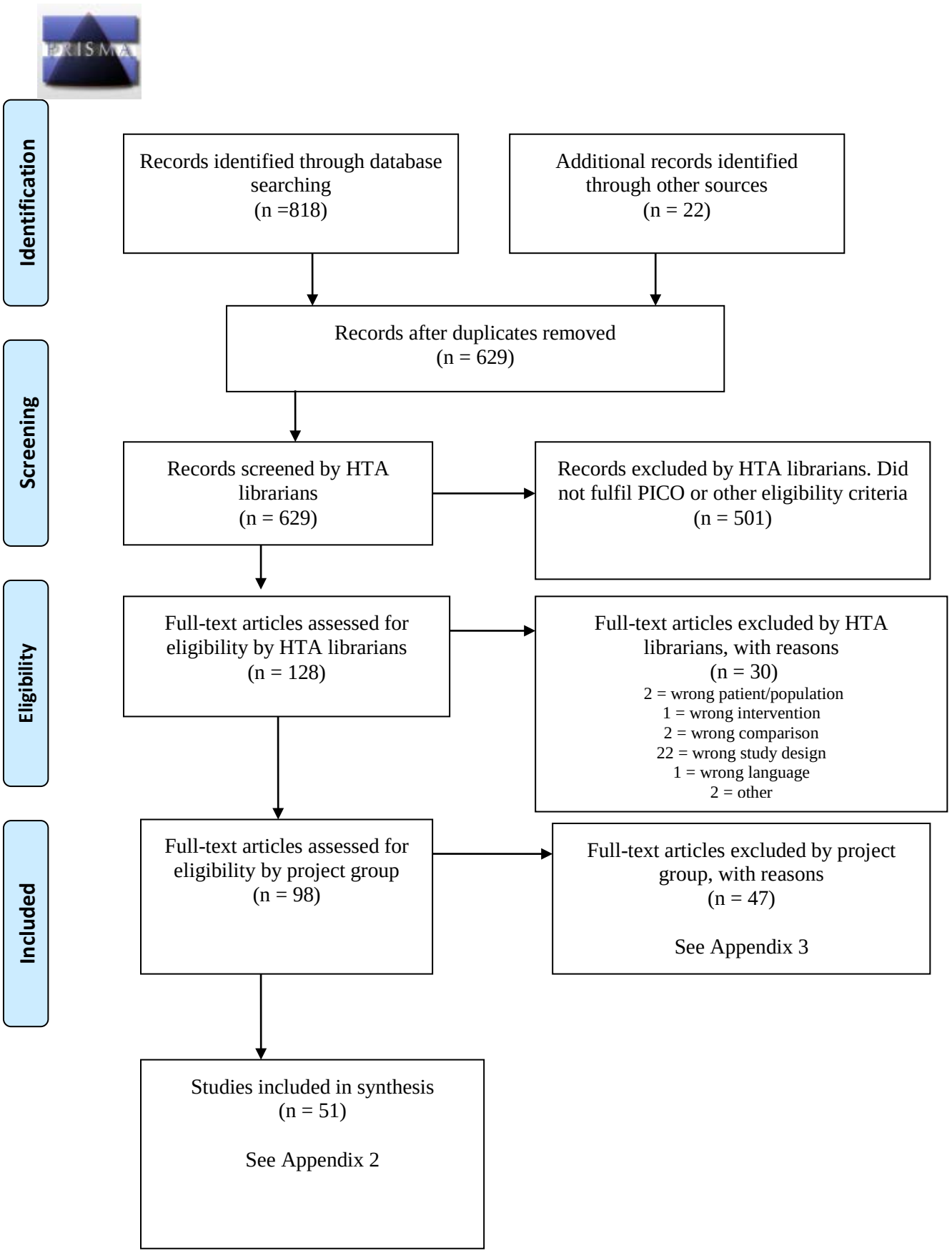
<u>Eligibility criteria</u>

Study design:
Randomised controlled trials
Non-randomised controlled trials
Case series if ≥ 200 patients (AlloDerm) and ≥ 20 for all other ADM or matrices/meshes.

Year of publication:
2005-

Language:
English, Swedish, Danish, Norwegian

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2016-05-27
No of results: 489

#	Most Recent Queries	Result
#22	**Search #8 NOT #12 Filters: Publication date from 2005/01/01; Swedish; Norwegian; English; Danish**	**489**
#14	Search #8 NOT #12 Filters: Publication date from 2005/01/01	524
#13	Search #8 NOT #12	676
#12	Search #9 OR #10 OR #11	5843292
#11	Search animals[ti] OR animal[ti] OR rats[ti] OR rat[ti] OR mouse[ti] OR mice[ti]	1288050
#10	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4215235
#9	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1480954
#8	Search #4 AND #7	759
#7	Search #5 OR #6	406731
#6	Search mastectom*[tiab] OR mammaplast*[tiab] OR breast	405446
#5	Search Mastectomy[Mesh] OR Mammaplasty[Mesh]	32383
#4	Search #2 OR #3	19572
#3	Search strattice[tiab] OR veritas[tiab] OR alloderm[tiab] OR tigr[tiab] OR surgisis[tiab] OR permacol[tiab] OR Dermamatrix[tiab] OR neoform[tiab] OR FlexHD[tiab] OR Allomax[tiab] OR Surgimed[tiab] OR Vicryl[tiab] OR seri[tiab] OR adm[tiab] OR acellular dermal matrix OR acellular dermal matrices	7701
#2	Search Acellular Dermis[Mesh] OR Tissue Scaffolds[Mesh]	12440

Database: EMBASE (OVID SP)
Date: 2016-05-27
No of results: 261

#	Searches	Results
1	exp acellular dermal matrix/	1028
2	exp tissue scaffold/	10122
3	(strattice or veritas or alloderm or tigr or surgisis or permacol or Dermamatrix or neoform or FlexHD or Allomax or Surgimed or Vicryl or seri or adm or (acellular adj3 dermal adj3 matrix) or (acellular adj3 dermal adj3 matrices)).ti,ab,dv.	10971
4	1 or 2 or 3	21219
5	exp mastectomy/	44971
6	exp breast reconstruction/	16598
7	exp breast/	103376
8	(mastectom$ or mammaplast$ or breast).ti,ab.	444714
9	5 or 6 or 7 or 8	480697
10	4 and 9	914
11	(animal not (animal and human)).sh.	1325045
12	(animals or animal or rats or rat or mouse or mice).ti.	1499156

13	11 or 12	2579152
14	10 not 13	891
15	**limit 14 to (embase and (danish or english or norwegian or swedish) and yr="2005 - Current" and (article or conference paper or note or "review"))**	**261**

Database: The Cochrane Library
Date: 2016-05-27
No of results: 31
Cochrane reviews 1
Other reviews 4
Technology assessments 5
Economic evaluations 3
Clinical trials 18

ID	Search	Hits
#1	strattice or veritas or alloderm or tigr or surgisis or permacol or Dermamatrix or neoform or FlexHD or Allomax or Surgimed or Vicryl or seri or adm or acellular dermal matrix or acellular dermal matrices:ti,ab,kw (Word variations have been searched)	570
#2	MeSH descriptor: [Acellular Dermis] explode all trees	30
#3	MeSH descriptor: [Tissue Scaffolds] explode all trees	47
#4	#1 or #2 or #3	620
#5	MeSH descriptor: [Mastectomy] explode all trees	1442
#6	MeSH descriptor: [Mammaplasty] explode all trees	310
#7	mastectom* or mammaplast* or breast:ti,ab,kw (Word variations have been searched)	27157
#8	#5 or #6 or #7	27157
#9	**#4 and #8 Publication Year from 2005 to 2016**	**31**

Database: CRD
Date: 2016-05-27
No of results: 37
DARE 18
NHS EED 6
HTA 13

Line	Search	Hits
1	**(strattice or veritas or alloderm or tigr or surgisis or permacol or Dermamatrix or neoform or FlexHD or Allomax or Surgimed or Vicryl or seri or adm or acellular dermal matrix or acellular dermal matrices) FROM 2005 TO 2016**	**37**

The web-sites of **SBU** and **Kunnskapssenteret** were visited
2016-08-01
Nothing relevant to the question at issue was found

Reference lists

A comprehensive review of reference lists brought 22 new records

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Author, Year, Country	Study Design	Study Duration (years)	Study Groups; Intervention vs Control	Patients (n) Breasts (n)	Mean Age (years)	Radiotherapy (%) of patients	Type of surgery/ Comments	Outcome variables
Antony 2010 USA	Retrospective cohort BM	2004 - 2008	AlloDerm vs non-ADM	I: P=96 B=153 C: P=2025 B=2910	I: 44.5 C: 48.1	I: pre 15.6; post 11.1 C: pre 9.4; post 11.4	Two stage	Implant loss Infection All complications
Bardelli 2016 Italy	Retrospective cohort SM	2012-2013	Surgimesh-pet vs non ADM	I: P=63 B=70 C: P=133 B=136	I: 50 C: 52	I: pre; post 2.7 C: pre; post 9.8	One and two stage	Implant loss Infection
Chun 2010 USA	Retrospective cohort BM	2002-2008	AlloDerm vs non-ADM	I: P=NR B=269 C: P=NR B=146 No of patients in both groups =283	I: 47.0 C: 46.2	I: pre 8.2 post 5.9 C: pre 4.8 post 8.2 [a]	One and two stage	Infection
Clarke-Pearson 2016 USA	Retrospective cohort BM	2006-2011	AlloDerm vs non-ADM	I: P=291 B=465 C: P=141 B=217	I: 49 C: 49	I: pre 15.1 post 8.9 C: pre 2.1 post 24.8	ADM+silicon implant No ADM+ expander	Infection Complications (1 vs 2 stage)
Collis 2012 USA	Retrospective cohort BM	2005-2009	AlloDerm vs non-ADM	I: P=63 B=106 C: P=42 B=68	I: 53 C: 53	I: NR C: NR	One and two stage	Implant loss Complications
Colwell 2011 USA	Retrospective cohort BM	2006-2010	AlloDerm vs non-ADM	I: P=211 B=331 C: P=NR B=158	I: 49 C: 50	I: pre 15.6 post 8.5 C: pre NR post NR [b]	ADM+silicon implant No ADM+ expander	Implant loss Infection Complications
Davila 2013 USA	Retrospective cohort BM	2006-2010	ADM vs non-ADM	I: P=NR B=1717 C: P=NR B=7442 N (in both groups) =9159	I: 50.6 C: 51	I: pre NR post 0.3 C: pre NR post 0.3	Expander vs no expander	Implant loss Infection Complications
Endress 2012 USA	Retrospective cohort SM	2008-2010	Surgimend vs non-ADM	I: P=28 B=49 C: P=91 B=123	I: 47 C: 49.5	I: pre /post 28.6 C: pre/post NR	Two stage	Implant loss Infection Complications
Forsberg 2014 USA	Retrospective cohort BM	2005-2009	ADM vs non-ADM	I: P=NR B=58 C: P=NR B=125 No (in both groups) =122	I: 49.7 C: 50.7	I: pre /post1 21.6 C: pre/post 18.8	Two stage	Implant loss Infection Aesthetics Complications

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Author, Year, Country	Study Design	Study Duration (years)	Study Groups; Intervention vs Control	Patients (n) Breasts (n)	Mean Age (years)	Radiotherapy (%) of patients	Type of surgery/ Comments	Outcome variables
Frey 2015 USA	Retrospective cohort BM	2010-2014	ADM/fenestrated ADM vs non-ADM	I: P=NR B=374 C: P=NR B=645 No of patients in both groups =620	I: 49 C: 51	I: pre 6.7 post 5.9 C: pre 7.3 post 10.4 [c]	One and two stage	Implant loss Infection
Ganske 2013 USA	Retrospective cohort BM	2008-2010	ADM vs non-ADM	I: P=NR B=106 C: P=NR B=73	I: 50.9 C: 46.8	I: pre 8.2 post 11.0 C: pre 14.2 post 9.4 [a] [c]	TE or implants	Infection Complications
Ibrhaim 2015 USA	Retrospective cohort BM	2005-2011	ADM vs non-ADM	I: P=3283 B=NR C: P=15714 B=NR	I: 50.7 C: 51.3	I: pre 0.3 post NR C: pre 0.4 post NR	Immediate or delayed TE or implants	Infection Complications
Israeli Ben-Noon 2013 Israel	Prospective cohort BM	NR	ADM vs non-ADM	I: P=16 B=24 C: P=16 B=23	I: 43 C: 42.8	I: pre 6.2 post NR C: pre 37.5 post NR	Immediate prosthetic BR	Infection Complications
Kilchenman 2014 Switzerland	Prospective cohort BM	2006-2011	ADM vs non-ADM	I: P=25 B=NR C: P=27 B=NR	I: 49.5 C: 48.6	I: pre 12.0 post 48.0 C: pre 29.6 post 40.7	ADM + implant. TE. LD+implant. LD+TE.	Implant loss Complications Data only on ADM + implant. TE
Liu 2011 USA	Retrospective cohort BM	2004-2009	ADM vs non-ADM	I: P=192 B=266 C: P=151 B=204	NR	I: pre /post 9.8 C: pre/post 10.4 [c]	Prosthetic breast reconstruction with or without ADM	Implant loss Infection Complications
Liu 2014 USA	Retrospective cohort BM	2006-2011	Alloderm vs FlexHD vs dermal graft	I: P=NR B=269 C: P=NR B=177 No of patients in both groups =382	48.5	I: pre /post1 1.8 C: pre/post NR [c]	Implant based BR. Immediate and delayed; TE and implants	Implant loss Infection Complications
Meyer Ganz 2015 Switzerland	Retrospective cohort SM	2002-2010	Submuscular vs vicryl mesh	I: P=NR B=115 C: P=NR B=46 No of patients in both groups =139	Mesh: 52.5 No mesh: 53	I: pre 1.7 post 6.1 C: pre 8.7 post 2.2 [c]	SSM with immediate breast reconstruction	Implant loss Infection Complications
Nguyen 2012 USA	Retrospective cohort BM	NR	ADM vs non-ADM	I: P=62 B=NR C: P=53 B=NR	I: 28.5 C: 25.6	I: pre 4.8 post 21.0 C: pre 9.4 post 22.6	Two stage only	Infection Aesthetics

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Author, Year, Country	Study Design	Study Duration (years)	Study Groups; Intervention vs Control	Patients (n) Breasts (n)	Mean Age (years)	Radiotherapy (%) of patients	Type of surgery/ Comments	Outcome variables
Nguyen 2010 USA	Retrospective cohort BM	1998-2008	Alloderm vs non-ADM	I: P=163 B=246 C: P=41 B=75	I: 49.1 C: 47.7	I: pre /post1 37.3 [c] C: pre/post 28.0	Unclear. a mix of one and two stage	Implant loss Infection
Parks 2012 USA	Retrospective cohort BM	2001-2011	Alloderm vs non-ADM	I: P=232 B=346 C: P=114 B=165	I: 50.6 C: 51.9	I: pre /post1 7.8 C: pre/post 22.4 [c]	Two stage	Implant loss
Peled 2012 USA	Retrospective cohort BM	2006-2010	Alloderm (consecutive/selective) vs non-ADM	I: P=225 B=360 C: P=63 B=90	I: 47.4 C: 44.6	I: pre 10.2 post 20.9 C: pre 4.4 post 23.3	Two stage	Implant loss Infection
Potter 2015a UK	Retrospective cohort BM	2011-2012	Technoss Protexa vs non-ADM	I: P=20 B=31 C: P=11 B=15	I: 50 C: 52	I: pre /post 30.0 C: pre/post 0.0	Mix of one and two stage	Implant loss Infection Complications
Preminger 2008 USA	Retrospective cohort BM	2004-2005	Alloderm vs non-ADM	I: P=NR B=45 C: P=NR B=45	I: NR C: NR	I: pre 13.3 post NR C: pre 13.3 post NR [a] [c]	Two stage	Complications
Sbitany 2009 USA	Retrospective cohort BM	2004-2007	Alloderm vs non-ADM	I: P=50 B=92 C: P=50 B=84	I: 48.6 C: 51.7	I: pre N post 12.0 C: pre N post 8 [a]	Two stage	Implant loss Complications
Sbitany 2016 USA	Retrospective cohort BM	2012-2013	Alloderm vs non-ADM	I: P=NR B=89 C: P=NR B=113	I: + C: 48 All patients	I: + C: pre 11.0 I: + C: post 34.0	Two stage	Implant loss Complications
Seth 2012 USA	Retrospective cohort BM	2006-2008	Alloderm /FlexHD vs non-ADM	I: P=137 B=199 C: P=280 B=393	I: 49.5 C: 47.4	I: pre 4.5 post 24.6 C: pre 6.4 post 18.9 [c]	Two stage	Implant loss Infection Complication vs radiation
Vardanian 2011 USA	Retrospective cohort BM	2000-2008	Alloderm vs non-ADM	I: P=123 B=208 C: P=80 B=129	I: 49 C: 47	I: pre N post N R C: pre N post NR	Unclear. a mix of one and two stage	Infection Aesthetics Complications
Winocour 2015 USA	Retrospective cohort BM	2005-2011	ADM vs non-ADM	I: P=2030 B=NR C: P=10396 B=NR	NR	I: pre N post NR C: pre N post NR	NR	Infection

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Author, Year, Country	Study Design	Study Duration (years)	Study Groups; Intervention vs Control	Patients (n) Breasts (n)	Mean Age (years)	Radiotherapy (%) of patients	Type of surgery/ Comments	Outcome variables
Barber 2015 UK	Case series BM	2008 - 2012	I:Strattice/Permacol/Alloderm	P=147 B=232	NR	NR	Mix of one and two stage	Implant loss Infection
Butterfield 2013 USA	Case series SM	2005-2010	I:Surgimend/Alloderm	P=281 B=440	~48	I: pre 7.1 post 9.6	Mix of one and two stage	Implant loss Complications
Dikmans 2016 Netherlands	Case series BM	2010-2014	I=Strattice	P=88 B=110	50.0	I: pre 9.1 post 17.05	One stage	Implant loss Infection Complications
Dieterich 2013 Germany	Case series SM	2008-2011	I:TiLOOP	P=207 B=231	47.0	OR=0.428 p=0.437	Mix of one and two stage	Complications
Eichler 2015 Germany	Case series SM	2008-2013	I:Surgimend/Epiflex	P=100 B=127	~55	I: pre /post1 20.6	NR	Implant loss Infection Complications
Gunnarsson 2013 Norway	Case series Unspec mesh	2011-2013	I: ADM unspec	P=59 B=76	51.0	NR	Mix of one and two stage	Implant loss Infection Complications
Hanna 2016 USA	Case series Unspec mesh	2008-2014	I: ADM unspec	P=217 B=323	51.0	I: pre 17.0 post 10.8	Two stage	Implant loss Infection
Headon 2016 UK	Case series SM	2012-2014	I:Surgimend	P=118 B=NR	50.1	I: pre 9.1 post 18.6	Mix of one and two stage	Implant loss Infection Complications Aesthetics
Hille-Betz 2015 Germany	Case series BM	2009-2013	I:Strattice	P=127 B=156	NR	I: pre 26.9 post 2.6	Mix of one and two stage	Implant loss Infection Complications
Hunsicker 2016 USA	Case series BM	2001-2014	I:Alloderm/Strattice/FlexHD	P=863 B=1584	47.0	I: pre 5.1 post 17.0	One stage	Implant loss Infection Complications

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Lardi 2014 UK	Case series BM	2008-2010	I:Alloderm/Strattice	P=149 B=200	48.0	I: pre 2.0 post 38.3	Mix of one and two stage	Implant loss Infection Complications
Mitchell 2013 USA	Case series BM	2009-2013	I:Strattice	P=103 B=158	51.0	I: pre 15.5 post 22.3	Mix of one and two stage	Implant loss Infection Complications
Mofid 2012 USA	Case series BM	2009-2010	I:Veritas	P=54 B=93	50.5	I: pre/post 16.7	Mix of one and two stage	Implant loss
Ohkuma 2013 USA	Case series SM	2009-2011	I:Surgimend	P=65 B=95	50.9	I: pre 8.5 post 17.0	Two stage	Infection Complications
Palaia 2015 USA	Case series BM	2006-2011	I:Alloderm/FlexHD	P=450 B=603	53.4	I: pre/post 8.0	Two stage	Implant loss Infection Complications
Rawlani 2011 USA	Case series BM	NR	I:FlexHD	P=84 B=121	50.2	NR	Two stage	Implant loss Infection Complications
Rundell 2014 USA	Case series BM	2007-2010	I:Allomax	P=203 B=348	~47	NR	Mix of one and two stage	Implant loss Infection Complications
Salzberg 2011 USA	Case series BM	2001-2010	I:Alloderm	P=260 B=466	NR	NR	One stage	Implant loss Infection Complications
Salzberg 2013 USA	Case series BM	2008-2009	I:Strattice	P=54 B=105	NR	I: pre/post 5.7	One stage	Implant loss Infection Complications
Salzberg 2016 USA	Case series BM	2001-2014	I:Alloderm/FlexHD/Strattice	P=863 B=1584	47.0	I: pre/post ~10	One stage (unclear)	Capsular contraction
Seth 2013 USA	Case series BM	2006-2011	I:Alloderm/FlexHD	P=255 B=369	~51.0	I: pre 8.1 post 23.0 [c]	Two stage	Implant loss Infection Complications

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Spear 2012 USA	Case series BM	2004-2010	I:Alloderm	P=289 B=428	46.1	I: pre 4.0 post 13.1	Two stage	Implant loss Infection Complications (radiotherapy)
Tessler 2014 USA	Case series SM	2011-2012	I:Vicryl	P=50 B=76	50.6	I: pre 5.3 post 13.2 [c]	One stage	Implant loss Infection Complications

ADM=acellular dermal matrix, ADM unspec=acellular dermal matrix, not specified, LD=latissimus dorsi flap, TE=tissue expander, NR=Not reported, I=Intervention, C=Control, P=Patients, B=Breasts, BM= biological mesh, SM=synthetic mesh, Unspec mesh= unknown, not specified mesh

[a] mismatch between presented and calculated data [b] unclear if radiation data presented on total no of patients or ADM group [c] percentages calculated per breast

Appendix 3. Excluded articles

Study author, publication year	Reason for exclusion
Avraham, 2015	Risk factor analysis
Bank, 2013	Wrong outcome, endpoint economic evaluation
Brooke, 2012	Mixed population including delayed reconstruction
Buseman, 2013	Too few patients
Cicilioni, 2013	Too few patients
Colwell, 2014	Outcome from different surgical incisions, wrong outcome
De Blacam, 2012	Wrong outcome, cost analysis
Fine, 2015	Only 50% of patients reported (interim analysis)
Freeman, 2016	Mix of delayed and immediate breast reconstruction
Glasberg, 2012	Too few patients
Gschwantler-Kaulich, 2016	Too few patients, mix of biological and non-biological material
Hadad, 2015	Comparison of two surgical methods, too few patients
Hanna, 2013	Too few patients
Hill, 2012	Wrong outcome, risk factor analysis
Ibrahim, 2013	Mix of delayed and immediate reconstructions
Jansen, 2011	Wrong outcome, cost analysis
Johnson, 2013	Wrong outcome, cost analysis
Jordan, 2016	Wrong outcome, analysis of seroma only
Kim, 2015	Too few patients
Kobraei, 2012	Wrong outcome, risk analysis
Koltz, 2013	Too few patients,
Krishnan, 2014	Wrong outcome, cost analysis
Krishnan, 2013	Wrong outcome, cost analysis
Lanier, 2010	Wrong population, not subcutaneous mastectomy
Lee, 2012	Wrong population, breast conserving surgery
Lee, 2015	Wrong population (ADM vs LD)
Lee, 2016	Meta-analysis with too few patients in Alloderm groups
Leyngold, 2012	Majority of patients with delayed reconstruction
Lynch, 2013	Evaluation of dermal sling
Lynch, 2015	Comparison ADM vs dermal sling (no muscle pocket), too few patients

Appendix 3. Excluded articles

Study author, publication year	Reason for exclusion
McCarthy, 2012	Outcome postoperative pain
Mendenhall, 2015	Too few patients
Michelotti, 2013	Wrong outcome, seroma formation
Nahabedian, 2009	Mixed population including delayed reconstruction
Pannucci, 2013	Delayed procedures included
Pestana, 2013	Mix of delayed and immediate reconstruction, to few patients, risk analysis
Philips, 2014	Wrong outcome, analysis of antibiotic treatment
Potter, 2015b	Too few patients. Systematic review with inclusion < 20 ADM in a group
Ranganathan,2015	13% had delayed procedures, no separate results
Selber, 2015	Meta-analysis, wrong outcome
Skovsted, 2016	Wrong outcome, comparison of different ADM's
Tae, 2009	Breast conserving surgery
Valdatta, 2014	Systematic review
Weichman, 2012	Inconsistent data reporting
Weichman, 2013	Comparison of sterile vs non sterile ADM
Woo, 2016	Wrong population, only non-obese patients
Zhao, 2015	Too few patients. Study with < 20 ADM in a group

ADM= acellular dermal matrix
LD= Latissimus dorsi flap

Project: Breast reconstruction with acellular dermal matrix (ADM)
Appendix 4.1
Outcome variable: Implant loss

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Number of breasts n=	Results per patients		Results per breast		Pre/postoperative radiotherapy (%) (unless otherwise stated in Comments)		Comments	Directness *	Study limitations *	Precision *
				ADM	No ADM	ADM	No ADM	ADM	No ADM				
Antony 2010 USA	Retrospective cohort	2121	3063	NR	NR	9/153 5.9%	55/2910 1.9%	15.6/11.1	9.4/11.4		+	-	-
Baldelli 2016 Italy	Retrospective cohort	196	206	NR	NR	8/70 11.4%	7/136 5.1%	1.7/2.7	8.7/9.8		+	-	-
Collis 2012 USA	Retrospective cohort	63	106	NR	NR	6/106 5.7%	3/68 4.4%	NR	NR		+	-	-
Colwell 2011 USA	Retrospective cohort	211	331	NR	NR	5/331 1.5%	11/148 7%	15.6/8.5	NR	ADM=> single stage non-ADM two stage	+	-	-
Davila 2013 USA	Retrospective cohort	9159	9164	NR	NR	18/1717 1%	59/7447 0.8%	NR/0.3	NR/0.3		+	?	+
Endress 2012 USA	Retrospective cohort	119	172	NR	NR	1/123 1.9%	2/49 6.5%	28.6	NR	Pre- and postop RT not separately reported.	+	-	-
Forsberg 2014 USA	Retrospective cohort	122	183	NR	NR	3/58 5.4%	13/125 10.6%	21.6	18.8	Pre- and postop RT not separately reported. Not only immediate reconstructions	+	-	-
Frey 2015 USA	Retrospective cohort	620	1019	5/164 3.0%	8/645 1.2%	NR	NR	6.7/5.9	7.3/10.4	Comparison of three different ADM's	+	-	-
Kilchenmann 2014 Switzerland	Retrospective cohort	52	NR	3/25 12%	7/27 25.9%	NR	NR	12.0/48.0	29.6/40.7		+	-	-
Liu 2011 USA	Retrospective cohort	343	470	NR	NR	7/266 4.9%	5/204 2.5%	9.8	10.4	Pre- and postop RT not separately reported.	+	-	-

ADM= acellular dermal matrix; NR=not reported; RT= radiotherapy

Project: Breast reconstruction with acellular dermal matrix (ADM)
Appendix 4.1
Outcome variable: Implant loss

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Number of breasts n=	Results per patients		Results per breast		Pre/postoperative radiotherapy (%) (unless otherwise stated in Comments)		Comments	Directness *	Study limitations *	Precision *
				ADM	No ADM	ADM	No ADM	ADM	No ADM				
Liu 2014 USA	Retrospective cohort	382	547	NR	NR	16/262 6.1%	10/177 5.6%	1.8	NR	Pre- and postop RT not separately reported. Mean follow up: 6.4 m	+	-	-
Meyer Ganz 2015 Switzerland	Retrospective cohort	139	161	NR	NR	7/112 6.3%	4/46 8.7%	1.7/6.1	8.7/2.2	Submuscular vs vicryl mesh	+	-	-
Nguyen 2010 USA	Retrospective cohort	204	321	NR	NR	6/75 8%	4/246 1.6%	37.3	28.0	Pre- and postop RT not separately reported.	?	-	-
Parks 2012 USA	Retrospective cohort	346	511	34/232 14.7%	11/114 9.7%	40/346 11.6%	14/165 8.4%	7.8	22.8	Pre- and postop RT not separately reported.	+	?	+
Peled 2012 USA	Retrospective cohort	280	450	NR	NR	20/360 5.6%	16/90 17.8	10.2/20.9	4.4/23.3	2 different surgical approach in ADM-group	+	-	?/-
Potter 2015a UK	Retrospective cohort	31	46	NR	NR	4/31 12.9%	2/15 13.3%	30.0	0	Pre- and postop RT not separately reported. All implant loss in ADM was preop radiated	+	?	-
Sbitany 2009 USA	Retrospective cohort	100	172	4/50 8%	3/50 6%	NR	NR	NR/12.0	NR/8.0	Numbers differ in article	+	-	-
Sbitany 2016 USA	Retrospective cohort	127	202	NR	NR	6/89 6.7%	9/113 7.9%	NR	NR		+	-	-
Seth 2012 USA	Retrospective cohort	417	592	NR	NR	17/199 8.5%	29/393 7.4%	4.5/24.6	6.4/18.9		+	-	?

ADM= acellular dermal matrix; NR=not reported; RT= radiotherapy

Project: Breast reconstruction with acellular dermal matrix (ADM)
Appendix 4.1
Outcome variable: Implant loss

* + No or minor problems
? Some problems
\- Major problems

Author year country	Study design	Results per patients NOT REPORTED		Results per breast		Comments
		ADM	No ADM	ADM	No ADM	
Barber 2015 UK	Case series			40/232 17.2%		
Butterfield 2013 USA	Case series			39/440 8.9%		
Dikmans 2016 Netherlands	Case series			11/110 10%		
Eichler 2015 Germany	Case series			0/63 0%		Surgimend
Eichler 2015 Germany	Case series			6/64 9.4%		Epiflex
Gunnarsson 2013 Norway	Case series			2/76 3%		
Hanna 2016 USA	Case series			38/323 11.8%		
Headon 2016 UK	Case series			2/164 1.2%		
Hille-Betz 2015 Germany	Case series			4/98 4.1%		
Hunsicker 2016 USA	Case series			46/1584 2.9%		
Lardi 2014 UK	Case series			25/200 12.5%		
Mitchell 2013 USA	Case series			13/158 8.2%		

Project: Breast reconstruction with acellular dermal matrix (ADM)
Appendix 4.1
Outcome variable: Implant loss

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Results per patients NOT REPORTED		Results per breast		Comments
		ADM	No ADM	ADM	No ADM	
Mofid 2012 USA	Case series			2/93 2.1%		
Palaia 2015 USA	Case series			47/603 7.8%		
Rawlani 2011 USA	Case series			8/121 6.6%		
Rundell 2014 USA	Case series			2/348 0.6%		’Reconstruction failure’
Salzberg 2013 USA	Case series			4/105 3.8%		
Salzberg 2011 USA	Case series			6/466 1.3%		
Seth 2013 USA	Case series			23/369 6%		
Spear 2012 USA	Case series			6/361 1.7%		
Tessler 2014 USA	Case series			1/76 1.3%		

Project: ADM in breast reconstruction
Appendix 4.2a
Outcome variable: Infection

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Number of breasts n=	Results per patients		Results per breast		Comments	* Directness	* Study limitations	* Precision
				ADM	No ADM	ADM	No ADM				
Antony 2010 USA	Retrospective cohort	2121	3063	NR	NR	5/153 3.3%	37/2910 1.3%		+	-	-
Baldelli 2016 Italy	Retrospective cohort	196	206	6/63 10.0%	7/133 5.9%	NR	NR		+	-	-
Chun 2010 USA	Retrospective cohort	283	415	NR	NR	24/269 8.9%	3/146 2.1		+	?	-
Clarke-Pearson 2016 USA	Retrospective cohort	432	682	NR	NR	19/465 4.1%	9/217 4.2%		+	-	-
Colwell 2011 USA	Retrospective cohort	211	331	NR	NR	10/331 3%	9/158 5.7%	ADM+silicon implant No ADM+ exp	+	-	-
Davila 2013 USA	Retrospective cohort	9159	-	66/1717 3.8%	246/7442 3.3%	NR	NR		+	?	+
Endress 2012 USA	Retrospective cohort	119	172	NR	NR	2/49 4.1%	9//123 7.3%		+	-	-
Forsberg 2014 USA	Retrospective cohort	122	183	NR	NR	9/58 16.2%	7/125 5.9%	Not only immediate reconstructions	+	-	-
Frey 2015 USA	Retrospective cohort	620	1019	12/164 7.3%	24/645 3.7%	NR	NR	Comparison of three different ADM's	+	-	-
Ganske 2013 USA	Retrospective cohort		179	NR	NR	4/106 3.8%	0/73		+	-	-

NR=not reported

Project: ADM in breast reconstruction
Appendix 4.2a
Outcome variable: Infection

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Number of breasts n=	Results per patients		Results per breast		Comments	* Directness	* Study limitations	* Precision
				ADM	No ADM	ADM	No ADM				
Ibrahim 2015 USA	Retrospective cohort	3284 vs 15743	N	109/3284 3.3%	405/15742 2.6%	NR	NR		+	-	-
Israeli Ben-Noon 2013 Israel	Prospective cohort	32	47	NR	NR	2/24 8%	1/23 4.3%		+	-	-
Liu 2011 USA	Retrospective cohort	343	470	NR	NR	18/266 6.8%	5/204 2.5%		+	-	-
Liu 2014 USA	Retrospective cohort	NR	Total 547	NR	NR	31/288 10.7% (for ADM and Flex HD together)	7.3% 18/252	alloderm 175 FlexHD 113 dermal matrix 7 no matrix 252 Mean follow up: 6.4 m	+	-	-
Meyer Ganz 2015 Switzerland	Retrospective cohort	139	158	NR	NR	3/112 2.7%	1/46 2.2%	Submuscular vs vicryl mesh	+	-	-
Nguyen 2010 USA	Retrospective cohort	204	321	NR	NR	4/75 5.3%	7/246 2.8%		?	-	-
Peled 2012 USA	Retrospective cohort	280	450	NR	NR	25/90 27.8%	61/360 17%	2 different surgical approaches in ADM-group	+	-	?/-
Potter 2015a UK	Retrospective cohort	31	46	NR	NR	0/15 0%	2/31 6.5%		+	?	-
Seth AK 2012 USA	Retrospective cohort	417	592	NR	NR	14/199 7%	17/393 4.3%		+	-	?

NR=not reported

Project: ADM in breast reconstruction
Appendix 4.2a
Outcome variable: Infection

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Number of breasts n=	Results per patients		Results per breast		Comments	* Directness	* Study limitations	* Precision
				ADM	No ADM	ADM	No ADM				
Vardanian 2011 USA	Retrospective cohort	203	337	NR	NR	2/208 1%	3/129 2.3%		+	?/-	?/+
Winocour 2014 USA	Retrospective cohort	12163	NR	85/1890 4.5%	331/10273 3.2%	NR	NR		+	-	+

NR=not reported

* + No or minor problems
? Some problems
- Major problems

Project: ADM in breast reconstruction
Appendix 4.2b
Outcome variable: Infection

Author year country	Study design	Results per patients NOT REPORTED	Results per breast with ADM	Comments
Butterfield 2013 USA	Case series		17/351 4.8%	
Dieterich 2013 Germany	Case series		14/231 6.1%	
Dikmans 2016 Netherlands	Case series		13/110 11.8%	
Eichler 2015 Germany	Case series		0/63 0%	Surgimend
Eichler 2015 Germany	Case series		6/64 9.4%	Epiflex
Gunnarsson 2013 Norway	Case series		5/76 6.6%	
Hanna 2016 USA	Case series		38/323 11.8%	
Headon 2016 UK	Case series		2/164 1.2%	I princip implant loss
Hille-Betz 2015 Germany	Case series		3/98 3.1%	4/98 = implant loss 4.1%
Hunsicker 2016 USA	Case series		48/1584 3%	46/1584 = implant loss 2.9%
Lardi 2014 UK	Case series		23/200 11.5%	

* + No or minor problems
? Some problems
- Major problems

Project: ADM in breast reconstruction
Appendix 4.2b
Outcome variable: Infection

Author year country	Study design	Results per patients NOT REPORTED	Results per breast with ADM	Comments
Mitchell 2013 USA	Case series		9/158 5.7%	
Ohkuma 2013 USA	Case series		16/95 16.8%	
Palaia 2015 USA	Case series		59/603 9.8%	
Rawlani 2011 USA	Case series		9/121 7.4%	
Rundell 2014 USA	Case series		23/348 6.6%	
Salzberg 2013 USA	Case series		4/105 3.8%	
Salzberg 2011 USA	Case series		1/466 0.2%	
Seth 2013 USA	Case series		26/369 7%	
Spear 2012 USA	Case series		7/361 1.9%	
Tessler 2014 USA	Case series		1/76 1.3%	

Project: ADM in breast reconstruction
Appendix 4.3
Outcome variable: Total complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Number of breasts n=	Results per patients		Results per breast		Comments	* Directness	* Study limitations	* Precision
				ADM	No ADM	ADM	No ADM				
Antony 2010 USA	Retrospective cohort	2121	3063	NR	NR	35/153 23.6%	360/2910 12.4%		+	-	-
Clarke-Pearson 2016 USA	Retrospective cohort	432	682	NR	NR	62/465 13.3%	26/217 12.0%	Major C	+	-	-
Collis 2012 USA	Retrospective cohort	63	106	NR	NR	20/106 18.9%	5/68 7.4%		+	-	-
Colwell 2011 USA	Retrospective cohort	211	331	NR	NR	50/331 14.8%	31/158 19.6%	Adm+silicon implant No adm+ exp	+	-	-
Davila 2013 USA	Retrospective cohort	9159	NR	95/1717 5.5%	394/7442 5.3%	NR	NR	Major complications 1.6 vs 1.5% respectively	+	?	+
Endress 2012 USA	Retrospective cohort	119	172	NR	NR	11/49 22.4%	16/123 13.0%		+	-	-
Forsberg 2014 USA	Retrospective cohort	122	183	NR	NR	19/58 32%	44/125 35%	Not only immediate reconstructions	+	-	-
Ganske 2013 USA	Retrospective cohort	NR	179	NR	NR	39/106 36.8%	5/73 6.8%		+	-	-
Ibrahim 2015 USA	Retrospective cohort	19027	NR	175/3284 5.3%	771/15743 4.9%	NR	NR		+	-	-
Israeli Ben-Noon 2013 Israel	Prospective cohort	32	47	NR	NR	8/24 33%	3/23 13%		+	-	-

NR=not reported

Project: ADM in breast reconstruction
Appendix 4.3
Outcome variable: Total complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Number of breasts n=	Results per patients		Results per breast		Comments	* Directness	* Study limitations	* Precision
				ADM	No ADM	ADM	No ADM				
Kilchenmann 2014 Switzerland	Prospective cohort	52	NR	12 /25 48% < 3 m	13/27 48.1% < 3 m	NR	NR	Unclear whether same patient had complication both before and after 3 m	+	-	-
Meyer Ganz 2015 Switzerland	Retrospective cohort	139	158	NR	NR	38/112 33.9%	19/46 41.3%	Submuscular vs vicryl mesh	+	-	-
Potter 2015a UK	Retrospective cohort	31	6	NR	NR	12/31 38.7%	6/15 40%	Early and major complications together	+	?	-
Preminger 2008 USA	Retrospective cohort	90	NR	7/45 15.6%	3/45 6.7%	NR	NR		+	-	-
Sbitany 2009 USA	Retrospective cohort	100	172	7/50 14%	9/50 18	NR	NR		+	-	-
Seth 2012 USA	Retrospective cohort	417	592	NR	NR	37/199 18%	56/393 14%		+	-	?
Vardanian 2011 USA	Retrospective cohort	203	337	NR	NR	61/208 29.3%	52/129 40.3%		+	?/-	?/+

NR=not reported

Project: ADM in breast reconstruction
Appendix 4.3
Outcome variable: Total complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Number of breasts n=	Results per patients		Results per breast		Comments	* Directness	* Study limitations	* Precision
				ADM	No ADM	ADM	No ADM				
Butterfield 2013 USA	Case series			NR		79/351 22.5%					
Dieterich 2013 Germany	Case series			NR		67/231 29%					
Dikmans 2016 Netherlands	Case series			69/88 78.4%		78/110 67.3%					
Eichler 2015 Germany	Case series			NR		7/63 11.1%		Surgimend			
Eichler 2015 Germany	Case series			NR		26/64 40.6%		Epiflex			
Gunnarsson 2013	Case series			NR		10/76 13%					
Headon 2016 UK	Case series			NR		7/164 4%					
Hille-Betz 2015 Germany	Case series			NR		29/98 29.6%					
Hunsicker 2016	Case series			NR		137/1584 8.6%					
Lardi 2014 UK	Case series			NR		65/200 32.5%					

NR=not reported

Project: ADM in breast reconstruction
Appendix 4.3
Outcome variable: Total complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Number of breasts n=	Results per patients		Results per breast		Comments	* Directness	* Study limitations	* Precision
				ADM	No ADM	ADM	No ADM				
Mitchell 2013 USA	Case series			NR		17/158 10.8%					
Ohkuma 2013 USA	Case series			NR		21/95 22.1%					
Palaia 2015 USA	Case series			NR		125/603 20.7%					
Rawlani 2011 USA	Case series			NR		20121 16.5%					
Rundell 2014 USA	Case series			NR		57/348 16.4%					
Salzberg 2013 USA	Case series			NR		9/105 8.6%					
Salzberg 2011 USA	Case series			NR		18/466 3.9%					
Seth 2013	Case series			NR		71/369 19%					
Tessler 2014 USA	Case series			NR		5/76 6.6%					

NR=not reported

Project: ADM in breast reconstruction
Appendix 4.4 Outcome variable: Aesthetics

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Number of patients n=	Number of breasts n=	Score*	Blinded evaluators n=	Results per patients (Overall outcome)		Comments	Directness *	Study limitations *	Precision *
						ADM	No ADM				
Forsberg 2014 USA	Retrospective cohort	122	183 (58 ADM 125 TSR)	1-5	18 (6 plastic surgeons 6 plastic residents 6 medical students)	3.60 3.82 3.92 4.09 3.2	2.46 3.56 3.76 3.96 3.6	Five different domains are evaluated and compared: -Natural contour p=0.14 -Shape symmetry p=0.004 -Size symmetry p=0.018 -Chest position p=0.09 -Overall aesthetic outcome p=0.005	+	-	-
Nguyen 2012 USA	Retrospective cohort	62 ADM 53 No ADM		0-2	3	1.38 1.11 1.39 1.38 1.23	1.11 0.92 1.57 1.36 1.39	Both breasts included in evaluation in each subject -Breast mound volume p=0.0102 -Contour p=0.0621 -Breast mound ns placement p=0.0217 -Scarring p=0.8055 -Inframammary fold p=0.0458	?	-	?
Vardanian 2011 USA	Retrospective cohort	203	337 (208 ADM 129 PSR/TSR)	1-4	4 (1 male surgeon 1 female secretary 2 female medical students)	3.26 3.35	2.87 2.94	-Overall aesthetic appearance + -Outcome of inframammary fold.p< 0.05	+	?-	?+

Score*; Higher number means imply better results. Results per breast are not reported.
ADM= acellular dermal matrix
TSR=Total Submuscular reconstruction
PSR=Partial Submuscular reconstruction

Project: ADM in breast reconstruction
Appendix 4.5
Outcome: Capsular contraction

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	Number of breasts n=	Results per breast		Follow up (mean months) ADM Non ADM	Comments	* Directness	* Study limitations	* Precision
				ADM	No ADM					
Baldelli 2016 Italy	Retrospective cohort	196	206	5/70 7.1%	6/136 4.4%	NR	Synthetic mesh	+	-	-
Clarke-Pearson 2016 USA	Retrospective cohort	432	682	21/465 4.5%	7/217 3.2%	NR		+	-	-
Forsberg 2014 USA	Retrospective cohort	122	183	5/58 8.6%	29/125 23.2%	24.6 33.8		+	-	-
Meyer Ganz 2015 Switzerland	Retrospective cohort	139	158	12/112 10.7%	3/46 6.5%	NR	Synthetic mesh	+	-	-
Vardanian 2011 USA	Retrospective cohort	203	337	8/208 3.8%	25/208 19.4%	NR		+	?/-	?/+
Salzberg 2011 USA	Case series	260	466	3/466 0.6%		28.9		Not evaluated		
Salzberg 2013 USA	Case series	NR	571	2/571 0.4%		41.3		Not evaluated		
Salzberg 2016 USA	Case series	863	1584	127/1584 0.8%		56.4		Not evaluated		
Spear 2012 USA	Case series	289	428	55/428 12.8%		15.2		Not evaluated		
Tessler 2014 USA	Case series	50	76	1/76 1.3%		16		Not evaluated		

ADM= acellular dermal matrix; NR= not reported

Appendix 5 Ongoing studies

NCT number	Title	Conditions	Interventions	URL
NCT 00616824	The Use of an Acellular Dermal Matrix in a Two-Staged Breast Reconstruction	Mastectomy|Postoperative Pain|Complications	Procedure: Dermamatrix to cover lateral aspect of tissue expander|Procedure: Serratus anterior to cover lateral aspect of tissue expander	https://ClinicalTrials.gov/show/NCT00616824
NCT 00692692	Use of Dermal Matrix in Breast Reconstruction	Breast Cancer	Procedure: DermaMatrix|Procedure: standard of care tissue expander breast reconstruction surgery after mastectomy	https://ClinicalTrials.gov/show/NCT00692692
NCT 02830685	Pre-pectoral Breast Reconstruction PART 1	Breast Cancer	Device: DTI with Acellular Dermal Matrix (CELLIS® Breast)|Device: DTI with Titanium Coated Polypropylene Mesh (TiLOOOP® Bra)	https://ClinicalTrials.gov/show/NCT02830685
NCT 02831426	Pre-pectoral Breast Reconstruction PART 2	Breast Cancer	Device: Two-stage with Acellular Dermal Matrix (CELLIS® Breast)|Device: Two-stage with Titanium Coated Polypropylene Mesh (TiLOOOP® Bra)	https://ClinicalTrials.gov/show/NCT02831426
NCT 02562170	Protexa® Versus TiLoopBra® in Immediate Breast Reconstruction- A Pilot Study	Breast Cancer|Hereditary Breast and Ovarian Cancer Syndrome	Device: TiLoop Bra|Device: Protexa	https://ClinicalTrials.gov/show/NCT02562170
NCT 02521623	SurgiMend® vs. Strattice™ in Direct to Implant Breast Reconstruction- A Prospective Randomized Trial	Breast Neoplasms	Device: SurgiMend® Acellular Dermal Matrix|Device: Strattice™ Acellular Dermal Matrix	https://ClinicalTrials.gov/show/NCT02521623
NCT 02891759	Compare Outcomes Between Two Acellular Dermal Matrices	Breast Cancer	Device: Alloderm RTU|Device: Cortiva 1mm Allograft Dermis|Procedure: Skin or nipple-sparing mastectomy (standard of care)|Other: Breast Q|Procedure: Surgery (to address the tissue expander) (standard of care)	https://ClinicalTrials.gov/show/NCT02891759
NCT 01310075	Bioprosthetic Mesh to Expand the Lower Pole in Tissue Expander Reconstruction	Breast Cancer	Device: Alloderm|Device: Surgimend	https://ClinicalTrials.gov/show/NCT01310075
NCT 02372305	Comparison of FlexHD and Alloderm Outcomes in Breast Reconstructive Surgery	Breast Neoplasm	Biological: FlexHD|Biological: Alloderm	https://ClinicalTrials.gov/show/NCT02372305
NCT 00956384	One-stage Breast Reconstruction Using Dermal Matrix/Implant Versus Two-stage Expander/Implant Procedure	Breast Cancer	Procedure: One-stage dermal matrix/implant procedure|Procedure: Two-stage tissue expander/implant procedure	https://ClinicalTrials.gov/show/NCT00956384
NCT 02985073	The Gothenburg **TIGR/Veritas®** Study - A Comparison Between Biological (**Veritas®**) vs Non Biological Mesh (**TIGR®**) in Immediate Breast Reconstruction	Hereditary breast cancer	Biological Veritas in one breast and synthetic TIGR in the opposite breast	https://ClinicalTrials.gov/show/NCT02985073

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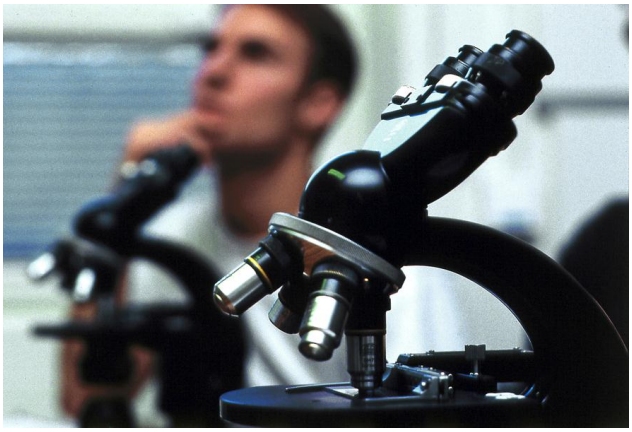
Health Technology Assessment
Regional activity-based HTA



HTA

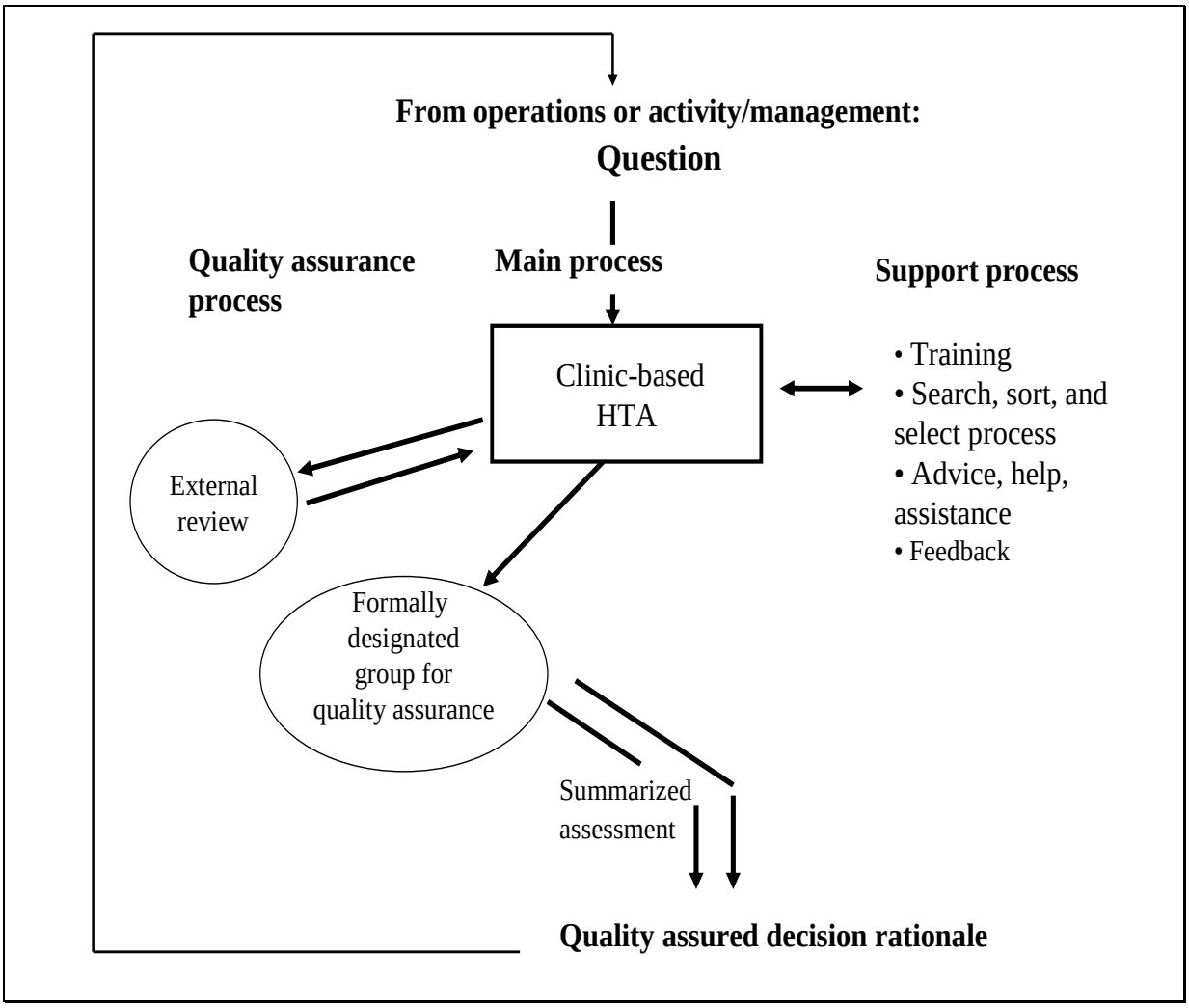
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale