Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1575 – Autologous fat grafting (AFG) by injection, for defects arising from breast surgery, breast cancer treatment / prevention and congenital breast deformity.

Applicant: **Breast Surgeons of Australia and New Zealand (BreastSurg ANZ)**

Date of MSAC consideration: **MSAC 79th Meeting, 28-29 July 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1.   Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of autologous fat grafting (AFG) injection for the treatment/management of defects arising from breast surgery, breast cancer treatment/prevention and congenital breast deformity was received from Breast Surgeons of Australia and New Zealand by the Department of Health.

2.   MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported public funding for AFG injection for the treatment/management of defects arising from breast surgery, breast cancer treatment/prevention and congenital breast deformity. MSAC noted limitations in the evidence, but considered that, on balance, the totality of evidence indicated that AFG is safe, cost-effective, and will have modest costs to the MBS while reducing out-of-pocket costs for patients. MSAC accepted that AFG is an established standard practice for treating and managing these patients. MSAC noted issues regarding the fee and potential leakage for cosmetic use, particularly in the congenital breast deformity population. MSAC recommended a review be conducted after 1 year to observe if leakage due to cosmetic use is occurring.

Consumer summary
Breast Surgeons of Australia and New Zealand applied for public funding via the Medicare Benefits Schedule (MBS) for the use of autologous fat grafting (AFG) for people who have breast defects as a result of breast surgery, breast cancer treatment or prevention, or who were born with certain breast deformities.

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Consumer summary
AFG is a type of surgery that takes fat from one part of the body (such as the thigh) using liposuction, and injects it into another part of the body (such as the breast). The transferred fat adds volume to the area it is injected into, which can help correct defects. Over time, the body absorbs some of the transferred fat, so AFG is usually done several times to reach the desired effect. MSAC noted that the clinical studies on AFG were low quality, making it difficult to be sure that AFG is safe and effective. After reviewing all of the available evidence, MSAC considered that, overall, AFG is safe, effective and cost-effective. MSAC noted the large number of comments from consumers and practitioners, which supported AFG. Consumers mentioned that AFG had benefits such as pain relief, minimal scarring and the convenience of a same-day procedure. MSAC also noted the psychological impact that breast defects due to cancer treatment or prevention can have on a person's wellbeing, and that the availability of effective treatment options can improve quality of life in these circumstances. MSAC noted AFG is already a standard practice for treating and managing these patients, so MBS listing will improve access to AFG services and reduce out-of-pocket costs for consumers. MSAC was concerned that people may try to use this MBS item to claim AFG services for cosmetic reasons, which is not funded under the MBS. To prevent this, MSAC decided to list the specific conditions that are covered under this item number, and to limit use of the item to certain types of specialists. MSAC recommended that the MBS item is reviewed after one year to check that it is being used properly. MSAC also asked the Department to look at the MBS fees for other breast-related procedures to make sure the proposed fee for AFG is in line with those, especially considering that the AFG fee can be claimed up to five times. **MSAC's advice to the Commonwealth Minister for Health** MSAC supported public funding for AFG for people with certain breast defects and breast surgeries. MSAC accepted that AFG was likely effective, safe and cost-effective. MSAC recommended review of use of the item after one year to check it is being used as intended.

3.   Summary of consideration and rationale for MSAC's advice

MSAC noted the application was requesting MBS listing for AFG injection for the management of defects arising from breast surgery, breast cancer treatment/prevention (Population A, with 3 subpopulations) and congenital breast deformity (Population B). MSAC noted this application arose from an MBS Review Taskforce recommendation and initially covered a broader population, which was split into MSAC Application 1575 and 1577. The linked MSAC Application 1577 is requesting MBS listing for AFG for the treatment of burn scars, and facial defects due to craniofacial abnormalities.

MSAC noted the extensive feedback from consumers and practitioners, which was supportive of the application. Consumers cited benefits of AFG including pain relief, minimal scarring and the convenience of a same-day procedure. Some consumers reported that they had received implants because they could not afford AFG. MSAC accepted that AFG is an established standard practice for treating and managing these patients, and acknowledged that

MBS listing may improve access to breast reconstruction options for patients in rural areas, or for those who are unsuitable for skin flap or prosthesis.

MSAC noted the issues raised by the Evaluation Sub-Committee (ESC), including the complex patient populations with difficulty to define a true comparator for each subgroup, low quality of evidence and uncertain comparative safety, but MSAC considered that although limited, the available evidence indicated AFG is safe in both patient populations. MSAC noted the clinical effectiveness studies indicated that AFG may reduce pain and analgesic use, and improve patient satisfaction (BREAST-Q scores) compared with best supportive care. MSAC noted the limited evidence on the duration of effect of AFG in both patient populations, and that the rate of fat resorption over time appears to vary widely and may contribute to uncertainty. MSAC concluded that, based on the limited evidence, AFG is likely to have superior effectiveness compared with best supportive care or reconstruction alone in most subpopulations for Population A. However, the clinical effectiveness of AFG is uncertain for Population B.

MSAC noted the applicant's pre-MSAC response, which agreed with the conclusions from ESC and reiterated the importance of psychological benefits from breast reconstruction procedures including AFG for women with breast defects due to cancer treatment or prevention.

MSAC considered that the outcomes in the economic evaluation and financial impact were uncertain due to the complex patient populations and subpopulations, and limited clinical evidence base. MSAC noted ESC's suggestion that the DCAR consider a cost-consequence analysis (CCA). However, the DCAR reasoned that a CCA could not be reasonably performed due to lack of data, but re-summarised the results of the economic evaluations disaggregating for outcomes and costs. For the budget impact, MSAC noted that Population A contributed most to the total cost in the budget impact (see Table 14).

Overall, MSAC considered that, on balance, the totality of evidence indicated that AFG is safe, cost-effective, and will have modest costs to the MBS while reducing out-of-pocket costs for patients.

MSAC noted the proposed item descriptor, and considered the number of 'services per side' should be restricted to five (instead of three) so that it is consistent across populations in this application and with MSAC application 1577. MSAC noted the potential for leakage for cosmetic use, particularly for Population B. MSAC considered that the item descriptor should specifically list the indications that relate to Population B to prevent broad interpretation, as proposed by the PICO Advisory Sub-Committee (PASC) and supported by ESC. The descriptor should also specify a requirement for photographic or other imaging evidence in the patient record. MSAC also considered that the ability to claim the MBS item should be limited to breast surgeons, and plastic and reconstructive surgeons. Using this limitation, it would be possible to monitor for leakage through the regular audits that occur in this group of specialists. MSAC recommended that the Department liaise with the relevant colleges about including such monitoring in regular audits. MSAC also recommended that a review be conducted after 1 year to observe if leakage due to cosmetic use is occurring.

MSAC noted the proposed fee of $641.85 for AFG is in line with regional area liposuction items, and although additional costs are associated with the AFG procedure compared with liposuction, MSAC considered the fee to be the upper limit of the fee price. MSAC also noted the fees associated with other breast-related procedures available to treat the proposed

populations, including mastectomy (fee of $528.30) and breast reconstruction with tissue expansion (fee of $1,088.35). While the costs of revisions and complications associated with other breast-related procedures was noted, MSAC raised concern that since AFG may be claimed up to five times per side this may create a cost differential between the total rebatable fee (and cost) to treat a patient with AFG and other breast-related procedures. MSAC considered that the potential cost differentials may create perverse incentives for providers. MSAC therefore recommended that the Department review the fees for other breast-related procedures and determine whether a more appropriate benchmark exists on which to base the AFG fee.

MSAC supported the following item descriptor:

Autologous fat grafting (harvesting, preparation and injection of adipocytes) as an independent procedure or in conjunction with another procedure, if:
(a) the autologous fat grafting is for
  (i)   correction of defects arising from treatment and prevention of breast cancer in patients with contour defects, ≥20% volume asymmetry, post-treatment pain or poor prosthetic coverage, up to a total of 5 services per side (for total treatment of a single breast), but only one service to be billed on a single occasion of service; OR
  (ii) preparation of post mastectomy thin/irradiated skin flaps in patients intending to have breast reconstruction, up to a total of 5 services per side (for total treatment of a single breast), but only one service to be billed on a single occasion of service; OR
  (iii) breast reconstruction in suitable patients, up to 5 services per side (for total treatment of a single breast), but only one service to be billed on a single occasion of service, OR
  (iv) correction of developmental disorders of the breast, up to 5 services per side (for total treatment of a single breast), but only one service to be billed on a single occasion of service.
(b) photographic and/or imaging evidence demonstrating the clinical need for this service is documented in patient notes.

MBS Fee: $651.50 Benefit 75%=$488.65

4.   Background

This is the first submission (Department Contracted Assessment Report [DCAR]) for AFG injection for the treatment/management of defects arising from breast surgery, breast cancer treatment/prevention and congenital breast deformity.

The initial proposal to introduce a new MBS item for AFG arose as a recommendation from the Medical Benefits Schedule Review Taskforce. The draft report from the Plastic and Reconstructive Surgery Clinical Committee (PRSCC) recommended a new MBS item for AFG for defects resulting from excision of a breast malignancy, for defects post-mastectomy, or for developmental abnormality. The Breast Cancer Surgery and Reconstruction Working Group, part of the PRSCC, noted that a new item would require an MSAC application and stated support for such an application. The report was endorsed for Government by the MBS Review Taskforce at their meeting on 14 and 15 May 2019 (MBSR-outcomes-14-15 May 2019).

There is another relevant application:
  • Application 1577– AFG for the treatment of craniofacial defects and burns scars.

5.   Prerequisites to implementation of any funding advice

The application indicated that regulatory requirements are not applicable to the proposed medical service. The DCAR noted that the autologous fat that is harvested and re-injected during the AFG intervention falls within the definition of autologous human cells and tissues (HCT) products excluded from some aspects of TGA regulation (TGA excluded autologous HCT). Exclusion from TGA regulation is not exclusion from all regulation. There is regulation by other bodies that is sufficient to mitigate possible risks that may arise as a result of manufacturing and using autologous HCT products that are excluded from TGA regulation.

Medical devices or equipment used for the manufacture of autologous HCT products (i.e. used to harvest, prepare and re-inject the autologous fat for the AFG intervention), may be regulated under the medical devices framework, where it is to be used for the treatment, diagnosis or modification of a patient's anatomy or physiological process. Such medical devices can be found listed on the Australian Register of Therapeutic Goods (ARTG; reference Table 12, p56 of the DCAR).

6.   Proposal for public funding

AFG is comprised of two parts:
- the harvesting and preparation of the autologous fat; and
- re-injection of the autologous fat into the breast of the donor after being minimally manipulated (such as centrifugation, flushing or washing).

The proposed MBS item descriptor and fee includes both parts of the intervention, see **Table 1**.

Table 1 Proposed MBS item descriptor

Category 3 – Therapeutic Procedures
Autologous fat grafting (harvesting, preparation and injection of adipocytes) as an independent procedure or in conjunction with another procedure, if:
(a) the autologous fat grafting is for
(i)   correction of defects arising from treatment and prevention of breast cancer in patients with contour defects, ≥20% volume asymmetry, post-treatment pain or poor prosthetic coverage, up to a total of 3 services per side (for total treatment of a single breast), but only one service to be billed on a single occasion of service; OR
(ii) preparation of post mastectomy thin/irradiated skin flaps in patients intending to have breast reconstruction, up to a total of 3 services per side (for total treatment of a single breast), but only one service to be billed on a single occasion of service; OR
(iii) breast reconstruction in suitable patients, up to 5 services per side (for total treatment of a single breast), but only one service to be billed on a single occasion of service, OR
(iv) correction of developmental disorders of the breast, up to 3 services per side (for total treatment of a single breast), but only one service to be billed on a single occasion of service.
(b) photographic and/or imaging evidence demonstrating the clinical need for this service is documented in patient notes
Multiple Operation Rule
(Anaes.)
MBS Fee: $641.85 Benefit 75%=$481.39

Source: Table 1, p24 of the DCAR.

The DCAR noted that applicant's proposed MBS item descriptor, was modified during the PICO[1] ratification process to address some of the concerns expressed by the PICO[1] Advisory

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[1] Population, Intervention, Comparator, Outcome

Sub-Committee (PASC; as shown in Table 1 above from the ratified PICO Confirmation). However, other recommendations and observations from PASC still need to be addressed. For example:

- the item does not describe the lifetime number of sessions a patient may have, as a patient may have multiple indications over time;
- a bilateral service item should be developed to align with other MBS items; and
- if AFG is listed, the item descriptor would need to clearly outline restriction, to avoid benefits being paid for cosmetic procedures.

The DCAR also noted that the item descriptor will need to align with any of the accepted recommendations from the MBS Taskforce Review of the Plastic and Reconstructive MBS items.

The pre-ESC response claimed that the issue of 'lifetime number of session' is mitigated by the maximum allowance of 3 services per side as stated in the item descriptor. The intention is that there would be a maximum of 3 sessions of AFG (i.e 3 operations per side, as there may be insufficient donor fat to do bilateral surgery at each operation), which may be separated by 3 or more months. The applicant however supported an increased allowance of additional sessions in special circumstances and acknowledge the need for a bilateral item service. The applicant also noted that the item descriptor states that the use of AFG is for correction of defects arising from treatment or prevention of breast cancer, which should exclude cosmetic indications but would welcome a restriction for cosmetic purposes if it was felt necessary to clarify this.

In the rejoinder, the assessment group clarified the issue of 'lifetime number of session' refers to the fact that a patient may move through the different population categories (i.e. they are not mutually exclusive), so they would be eligible for further AFG sessions if they moved from one of the surgical categories to another (e.g. from a post mastectomy pre reconstructive category to a post mastectomy post reconstruction category).

7.   Summary of public consultation feedback/consumer Issues

A letter in support of AFG was received from the Breast Cancer Network Australia (BCNA), the peak national organisation for Australians personally affected by breast cancer. The BCNA states it represents more than 120,000 individual members and 300 breast cancer support groups from across Australia. BCNA notes the difficulties their members face accessing breast reconstruction surgery, due to long waiting lists in some public hospitals, no access to reconstruction surgery in some regional and rural areas and high out-of-pocket costs in the private health system (reports of up to $18,000). The BCNA notes that AFG is evidence-based, already used in Australia and other countries and therefore supports MBS funding for AFG to provide an additional, affordable breast reconstruction option for all women who might benefit (Letter from BCNA in support of AFG).

In addition, 70 consultation responses (55 from specialists, 15 from consumers/patient support group) were received. The feedback from Specialists (55 responses) and Consumers including patient support groups (15 responses) are summarised below.

Summary of Specialist Comments
Some of the main benefits of the proposed medical service being funded were:
- Equitable access to this service for all eligible patients.
- Wider range of equitable options for patients requiring breast reconstructive surgery.

- Health funds will be able to cover added out-of-pocket expenses with MBS listing and more patients could have the option to be treated in a private hospital.
- Natural reconstructive surgery, creates more natural feel/look of breasts.
- Often less invasive, with very low complication rate.
- Minimal scarring compared to other procedures.
- It can result in avoiding the need for implants, which normally need replacing in future. Otherwise it can be used alongside implant surgery to improve results.
- It can replace flap reconstruction which is has a longer surgery and recovery.
- Improved psychological wellbeing of the patient and improved outcomes from having more affordable choices.
- For some patients this is the only suitable option for breast reconstruction.

The specialists considered that disadvantages of the service could include:
- Poor results from untrained clinicians.
- Complications of surgery.
- It needs an anaesthetic.
- Resorption of portion of fat graft.
- Failure to remedy cosmetic defect.
- The percentage of fat which will survive is unpredictable.
- Possible need for repeat surgery, it often requires more than one procedure to achieve adequate volume. Large volume fat transfers must be done in stages to minimise the risk of fat necrosis and oil cysts.
- Post-operative bruising of the donor site, which may preclude early return to work.
- Potential "marketing" vehicle for financially motivated and untrained practitioners – restriction must be tight to avoid misuse in the context of a cosmetic procedure.

One specialist considered that another benefit from having this intervention MBS funded, is that it may move more patients from the public system into private hospitals for the service. Other services that could be delivered were recommended for this service in the form of physiotherapy and/or occupational therapy for fitting of compression garments and/or bra post-operative. One specialist added that physiological support could be of benefit to patients as an additional service before and/or after this intervention.

One of the specialists considered the descriptor should be amended to read "correction of developmental and acquired disorders…" The same specialist also considered that the fee is relevant to a small volume fat transfer however; occasionally a high volume fat transfer is performed (pg 15). Another specialist considered that this proposed service is critical for patient-centred cancer care.

Some mention was made to the proposed population being clearer about Poland's syndrome, post radiotherapy and post thoracic surgery as inclusions. Almost all specialists commented that the item descriptor needs to ensure it could not be used in patients undergoing breast reconstruction for cosmetic purposes.

One specialist considered that AFG should be publically funded for women having their breasts reconstructed after implantation removal.

Summary of Consumer Comments

The views towards the benefits of the proposed medical service, were similar to those listed by the specialists, especially in regards to it improving the patients' physical and mental wellbeing. It was noted that it will improve equitable access to this option for many patients and that it being much less invasive than other major surgeries was comforting to patients.

One of the consumers especially considered that the proposed service will benefit patients' physical and mental wellbeing.

The risk of complications and additional surgeries were noted as a disadvantage by the consumers.

Consumers added that the following allied health could be considered as other beneficial services before and/or after the intervention: dietician, exercise physiologist.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention

AFG is the harvesting, preparation, and re-injection of autologous fat, with or without specialised fat grafting equipment. It includes live fat cells being harvested from a donor site on the patient, prepared in theatre by a variety of methods to separate and purify the fat cells, and injected back into the defective area. It relies on the fat stem cells remaining viable in the transferred site.

Description of Medical Conditions

AFG is proposed for use in two broad patient populations.

Population A
Patients who have had previous surgery for breast cancer treatment or risk reduction for the treatment of post mastectomy pain and/or to improve post mastectomy skin quality (with or without radiation therapy) with the following subpopulations:
- Subpopulation A1 - Post mastectomy without reconstruction.
- Subpopulation A2 - Post mastectomy with suboptimal outcomes after autologous or prosthetic reconstruction.
- Subpopulation A3 - Suboptimal outcomes following breast conserving surgery (BCS) for benign or malignant neoplasms.

Population B
Developmental breast abnormalities defined as congenital tuberous breast or unilateral hypomastia causing asymmetry with a >20% difference in the contralateral side.

Population A clinical management pathway

The current clinical practice for managing patients with breast cancer (or risk of breast cancer) in the absence of MBS listing of AFG is depicted in **Figure 1**.
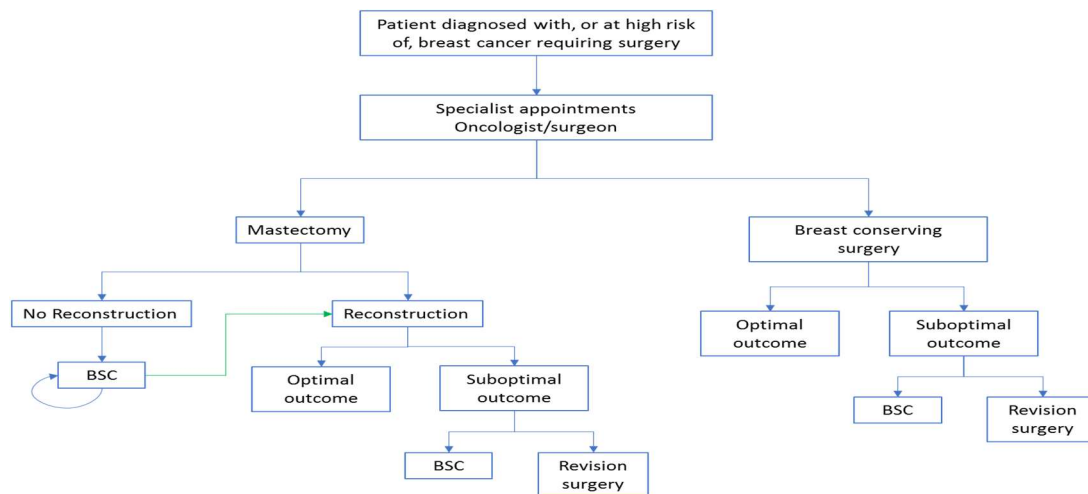

Figure 1 Current clinical management pathway of patients with breast cancer (or risk of breast cancer)
Note: the green line represents patients who initially elect to have no reconstruction but who have a change in preference over time. Patients who do not have reconstruction (because they are medically unfit) are unlikely to continue with best supportive care. PASC advised this should be tested in the sensitivity analysis.
Source: Figure 3, p87 of the DCAR.

The clinical management pathway is further broken down to present the current and proposed clinical management algorithms for the proposed subpopulations for public funding with AFG:
- Subpopulation A1: patients who are post mastectomy without reconstruction who are currently unable to pursue reconstruction. The availability of AFG will address the poor quality of their skin flaps, allowing them to have reconstruction with AFG alone or AFG treatment of skin flaps will allow for further prosthetic reconstruction. Additionally, those who are unable to pursue reconstruction may use AFG for the treatment of pain (Figure 2).

- Subpopulation A2: patients who are post mastectomy with reconstruction but have suboptimal outcomes is sub-divided into two subgroups: (i) those with skin flaps suitable for revision surgery and (ii) those with skin flaps that are not suitable for revision surgery. The availability of AFG would provide another option to have a breast reconstruction using AFG alone for those whose skin flaps are of a suitable quality or for those with poor quality skin, AFG will be used with further reconstructive surgery (Figure 3).
- Subpopulation A3: patients who have suboptimal outcomes following breast conserving surgery to their breast. The availability of AFG will present another option to the current options of best supportive care (BSC), mastectomy plus reconstruction or reduction mammoplasty of the contralateral breast. AFG may substitute for any of the current options or be an adjunct to the other surgical options (Figure 4).
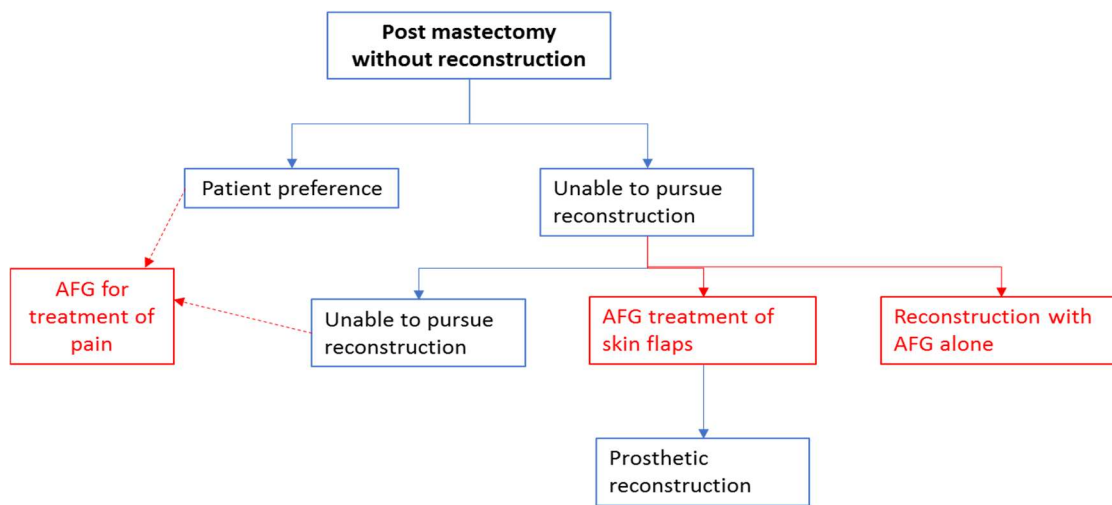

Figure 2 Current and proposed clinical management pathway of patients post mastectomy - Subpopulation A1
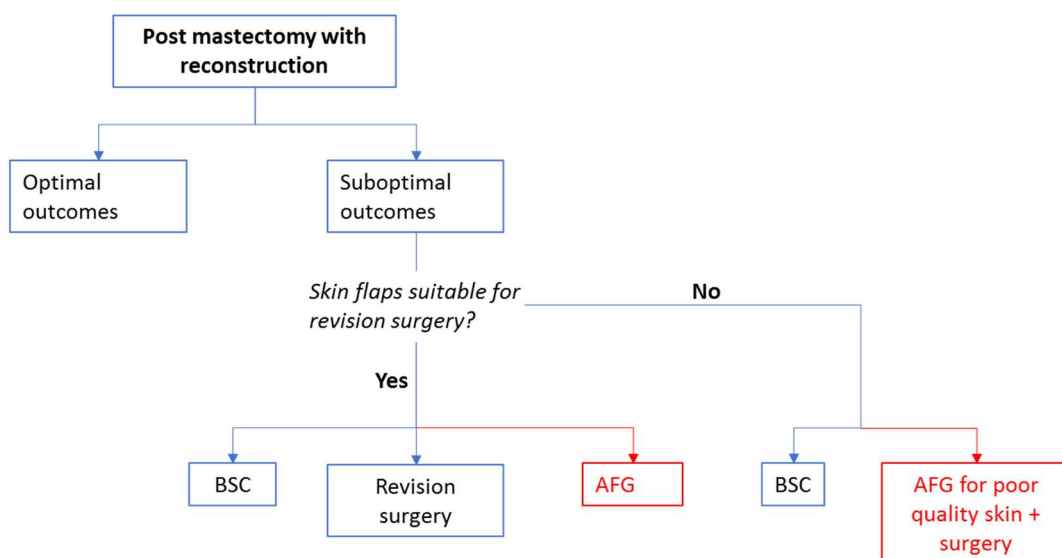Source: Figure 4, p87 of the DCAR.

Figure 3 Current and proposed clinical management algorithm for post mastectomy and post breast reconstruction patients - Subpopulation A2
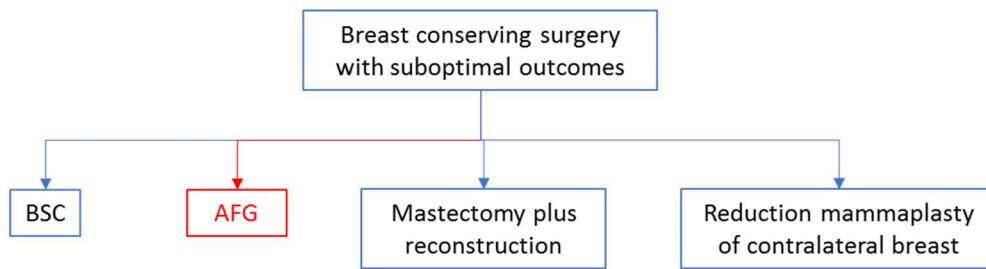Source: Figure 5, p88 of the DCAR.

Figure 4 Current and proposed clinical management of patients who have had suboptimal outcomes following breast conserving surgery - Subpopulation A3
Source: Figure 6, p89 of the DCAR.

Population B clinical management pathway

The current and proposed clinical management pathway for patients with developmental breast abnormalities, such as tuberous breasts, is depicted in **Figure 5**. AFG would provide an additional treatment option alongside currently available treatment of BSC or correction surgery. AFG could be used as a substitute or as an adjunct to other correction surgery.
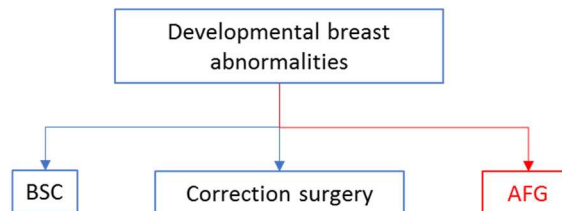

Figure 5 Current and proposed clinical management algorithm for patients with developmental breast abnormalities - Population B
Source: Figure 7, p of the DCAR.

9.   Comparator

The proposed comparators for AFG according to the patient populations are presented in Table 2**Error! Reference source not found.**, along with comments from the DCAR on differences between the ratified PICO Confirmation and DCAR. The DCAR noted BSC was not specified in the ratified PICO Confirmation; BSC was assumed in the DCAR to refer to analgesia for post mastectomy pain syndrome (PMPS).

The pre-ESC response acknowledged that the analysis of comparators is challenging in this application, and considered it was inappropriate that the DCAR seemed to have defaulted to BSC as the comparator for nearly every situation. In particular for Subpopulation A2, the applicant claimed 95% of patients are likely to have revisionary surgery. These patients may not have enough tissue volume to provide a completely autologous reconstruction, but would be suitable for flap surgery in combination with prosthetics, where prosthetic reconstruction alone has had a poor outcome. Therefore, the applicant stated that the use of BSC as the comparator for this group is inappropriate.

Table 2 Populations with their nominated comparators and consistency with clinical algorithms

Population	Comparator (as defined in Ratified PICO Confirmation)	Comments
Subpopulation A1: Patients who are post mastectomy without reconstruction (with or without radiation) who require AFG: a) AFG alone, to treat pain resulting from scarring and/or tightness of the skin following mastectomy; b) alone to construct a breast mound; or c) treatment of poor quality skin with AFG followed by prosthetic reconstruction.	a) BSC b) no reconstruction or alternative method of reconstruction; or c) no reconstruction or reconstruction with poor quality skin.	BSC not specified in the ratified PICO Confirmation, assumed in the DCAR to refer to analgesia for PMPS. Based on Figure 4 of the ratified PICO Confirmation, it appears that the comparator is patients unable to pursue reconstruction, not those for whom reconstruction (even with poor quality skin is an option). The definition of alternative method of reconstruction is not defined. DCAR assumes no reconstruction possible for both populations. Irradiated *vs.* non-irradiated skin has an effect on outcomes but clinical studies do not separate the populations by this characteristic.
Subpopulation A2: Patients who are post mastectomy with suboptimal outcomes following autologous or prosthetic reconstruction who require AFG: a) AFG alone, to treat pain resulting from scarring and/or tightness of the skin following mastectomy; b) alone to improve contour defects, volume differences and rippling; or c) as an adjunct to additional surgery to improve skin flaps to extend coverage of a prosthesis.	a) BSC; b) BSC or revision surgery c) BSC	BSC not specified in the ratified PICO Confirmation, assumed in the DCAR to refer to analgesia for PMPS. Figure 5 of the ratified PICO Confirmation separates out this Subpopulation according to whether their skin flaps are suitable for revision surgery. This is used to inform the comparators. For those who do have skin flaps suitable for revision surgery then the comparator is BSC or revision surgery. For those whose skin flaps are not suitable for revision surgery then the comparator is BSC. BSC is not defined.
Subpopulation A3: Patients with suboptimal outcome following breast conserving surgery for benign or malignant neoplasms who require AFG: a) AFG alone, to treat pain resulting from scarring and/or tightness of the skin following mastectomy; or b) alone to improve contour defects, volume differences and rippling.	a) BSC; b) BSC; or Mastectomy and reconstruction, or Contralateral breast reduction to correct asymmetry, or Other corrective surgery (e.g. local perforated flaps).	BSC not specified in the ratified PICO Confirmation, assumed in the DCAR to refer to analgesia for PMPS. Figure 6 of the ratified PICO Confirmation presents current comparators as (i) BSC; or (ii) Mastectomy plus reconstruction; or (iii) Reduction mammoplasty of contralateral breast, but excludes 'other corrective surgery'. The DCAR includes 'other corrective surgery' as one of the comparators (where evidence is available).
Population B: Patients with developmental breast abnormalities defined as: a) congenital tuberous breasts; or b) unilateral hypomastia causing asymmetry with a >20% difference to the contralateral side.	BSC; or Corrective breast surgery.	Figure 7 of the ratified PICO Confirmation is consistent, presenting the comparator as: • BSC; or • Correction surgery.

Abbreviations: AFG = autologous fat grafting; BSC = best supportive care; PMPS = post mastectomy pain syndrome.
Source: Table 2, p26 of the DCAR.

The DCAR listed the relevant MBS item for reimbursement of comparators to AFG according to their purpose:
- Mastectomy (31519, 31524)
- Breast reconstruction using autoflaps (45530, 45533, 45536)
- Breast reconstruction using prostheses (45527, 45539, 45542)
- Flap revision (45497, 45498, 45499)
- Augmentation mammoplasty (45524, 45528)
- Reduction mammaplasty (45520)
- Congenital developmental abnormalities (45528, 45060, 45061, 45062, 45556).
- Scar revision (45515, 45506 to 45518).

The DCAR also noted that these items may not always be the items charged and that the descriptors for these items remains in flux since being reviewed (MBSRT PRSCC 2018). The review found many items did not reflect current procedures, new item numbers were required and there is coding confusion between breast reconstruction and plastic reconstruction items.

10.   Comparative safety

A total of 35 comparative studies and five systematic reviews were included in the DCAR (see Table 3 for summary of evidence for Population A and **Table 4** for Population B below).

The DCAR identified a number of studies that reported on the use of AFG for the treatment of PMPS. Given the use of AFG for PMPS (i.e. for the reduction of pain) and the nominated comparator (BSC) is the same, regardless of where a patient may be in their reconstruction journey (defined as Subpopulations A1-A3), the evidence relating to AFG for the treatment of PMPS was presented together (see Table 3 below).

The DCAR noted that one comparative study (RCT; Juhl 2016[2]) assessed the use of AFG in patients who were post mastectomy without reconstruction (Subpopulation A1) and reported on the use of AFG for the treatment of post mastectomy pain (PMPS subpopulation). The DCAR elected to include this study (Juhl 2016) as part of the PMPS subpopulation.

The DCAR included the four studies (Calabrese 2018[3], Cuomo 2014[4], Ribuffo 2013[5], Vaia 2018[6]) in Subpopulation A1, as they included patients who do not have a completed reconstruction and are considered to be distinct from those who have a completed reconstruction (Subpopulation A2). However, the DCAR acknowledged that this group may be considered as those who have undergone reconstruction (Subpopulation A2). The DCAR suggested that MSAC may wish to consider whether this population is reflective of Subpopulation A1, or whether they should be considered as part of Subpopulation A2; alternatively, they may be considered to not represent any of the subgroups nominated in the ratified PICO Confirmation.

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[2] Juhl AA, Karlsson P, Damsgaard TE (2016) Journal of Plastic, Reconstructive and Aesthetic Surgery. 69(9):1192-202.

[3] Calabrese C, Kothari A, Badylak S, Di Taranto G, Marcasciano M, Sordi S, et al. (2018) European Review for Medical and Pharmacological Sciences. 22(15):4768-77.

[4] Cuomo R, Zerini I, Botteri G, Barberi L, Nisi G, D'Aniello C (2014) In Vivo. 28(5):993-6.

[5] Ribuffo D, Atzeni M, Guerra M, Bucher S, Politi C, Deidda M, et al (2013) Aesthetic Plastic Surgery. 37(6):1146-52.

[6] Vaia N, Lo Torto F, Marcasciano M, Casella D, Cacace C, De Masi C, et al. (2018) Aesthetic plastic surgery. 42(4):986-94.

f AFG for Population A

...etail	Intervention group	Comparator group	Risk of bias[b]	Outcomes[c]
...stectomy for treating breast ...r without radiotherapy, no ... Patients must have had ≥3 pain ...n the area of missing breast for ≥3	AFG to the pain-inflicted area around the missing breast	BSC (usual pain management)	Medium-high	Pain outcomes Scar outcomes
...severe scar retraction and PMPS. ...ad undergone mastectomy with ...ction and radiotherapy. All patients ...c reconstruction	Patients with PMPS who had been treated with AFG	Patients with PMPS who had not been treated with AFG	High	Pain outcomes **Analgesic use**
...severe scar retraction, ...y, and chronic pain meeting the ...PMPS", who had undergone ...with axillary dissection or BCS ...omy) followed by radiotherapy ...s same mastectomy patients as ...11 and Maione 2014	Patients with PMPS who had been treated with AFG	Patients with PMPS who refused treatment with AFG	High	Pain outcomes **Analgesic use**
...had undergone BCS ... and radiation therapy were ...r treatment of PMPS	AFG	Patients who did not undergo any further surgical procedure	High	Pain outcomes
...nosed for breast cancer, who ...SM with two-stage breast ...n	AFG at the time of second stage reconstruction (during the expander/ implant exchange) Two groups: (1) AFG enriched with SVF (SVF+AFG) and (2) standard (Coleman) AFG	No AFG (did not require it) at the time of second stage reconstruction (during the expander/ implant exchange)	Medium-high	Locoregional recurrence Systemic recurrence
...ho had radical mastectomy ...y dissection in order to treat ..., with prosthetic reconstruction	AFG in conjunction with prosthetic reconstruction	Prosthetic reconstruction alone	High	Pain outcomes Analgesic use Complications
...underwent total MRM and ...hi immediately elective mast...	AFG on irradiated expanders at ...t 6 weeks after...	Those who underwent immediate implantation of an...	High	Patient satisfaction **Reconstruction failure**

Author	Design	N[a]	Population detail	Intervention group	Comparator group	Risk of bias[b]	Outcomes[c]
Vaia 2018	C, NM, R	30	Patients who underwent modified radical mastectomy with immediate breast reconstruction with expanders	Patients who underwent modified radical mastectomy with immediate breast reconstruction with expanders, undergoing radiation therapy and AFG	Patients who underwent modified radical mastectomy with immediate breast reconstruction with expanders, not undergoing radiation therapy or AFG	High	Tissue thickness
Subpopulation: A2							
Bennett 2017	C, NM, R	2,048	Unilateral or bilateral mastectomy for treatment or prophylaxis (of the non-disease breast) of breast cancer, with or without radiotherapy, autologous or prosthetic reconstruction (breast mound reconstructed by Year 1)	Those who had AFG between Years 1 and 2. Reason for AFG treatment not reported (e.g. pain or suboptimal outcomes)	Those who had no AFG between Years 1 and 2 (but could have had AFG in post-operative Year 1)	High	BREAST-Q scores
Cogliandro 2017	C, NM, P	70	Patients selected to undergo definitive implant-based breast reconstruction. All patients developed different grades of breast asymmetry, resulting in dissatisfaction from an aesthetic point of view	Patients who underwent secondary AFG almost 1 year after prosthesis-based reconstruction	Patients who declined to undergo secondary AFG after prosthesis-based reconstruction	Low-medium	BREAST-Q scores
Fertsch 2017	C, M, R	200	Breast cancer patients treated with total mastectomy and delayed DIEP-flap reconstruction. Patients were not allowed to have a cancer recurrence between the time interval of their primary surgery (mastectomy), delayed DIEP-flap reconstruction and AFG	AFG following delayed DIEP-flap reconstructive surgery. Reason for AFG treatment not reported (e.g. pain or suboptimal outcomes)	No AFG following delayed DIEP-flap reconstructive surgery (matched to cases)	Low-medium	Disease-free survival
Kim 2014	C, NM, R	551	Patients with a history of breast cancer and reconstruction (autologous and prosthetic)	Those who underwent AFG for secondary revision breast surgery	Those who did not undergo AFG	Medium-high	Locoregional recurrence AFG complications (fat necrosis & cyst formation)
Lakhiani 2014	C, NM, R	23 (39)	Patients who underwent secondary breast augmentation with AFG or implant insertion or both, after post mastectomy autologous (free flap) reconstruction	AFG alone AFG + prosthesis	Prosthesis alone	High	**Aesthetic assessment** AFG complications (fat necrosis) surgical revisions (implant malpositioning)
Laporta 2015	C, M, P	40	Consecutive patients who received breast reconstruction with a DIEP flap	Reconstruction with an AFG-augmented DIEP flap	Reconstruction with a DIEP flap and no AFG (because of adequate abdominal donor-site volume)	Medium-high	Aesthetic assessment Locoregional recurrence Revision procedures; total treatment period

Author	Design	N[a]	Population detail	Intervention group	Comparator group	Risk of bias[b]	Outcomes[c]
Leuzzi 2019	C, NM, R	90 (95)	Patients who had undergone breast reconstruction with a LD flap (immediate or delayed, unilateral or bilateral)	Reconstruction with an LD flap and AFG	Reconstruction with an LD flap and prosthesis	High	**BREAST-Q scores (standardised point difference)** Revision procedures; total treatment period Surgical complications (infection, seroma, haematoma)
Masia 2015	C, NM, R	207 (214)	Consecutive patients who underwent mastectomy for breast cancer, with or without radiation therapy, and subsequent autologous reconstruction (free flaps)	Autologous (free-flap) reconstruction with subsequent AFG. Reason for AFG treatment not reported (e.g. pain or suboptimal outcomes)	Autologous (free-flap) reconstruction without subsequent AFG	Low-medium	Locoregional recurrence
Panettiere 2009	C, NM, P	61 (62)	Patients undergoing mastectomy, with radiation for breast cancer and subsequent prosthetic reconstruction. All patients presented mild to severe superficial irregularities and different degrees of skin dystrophy	AFG	No AFG, standard treatment only.	Low-medium	LENT-SOMA (pain, tele-angiectasias, atrophy, breast oedema, fibrosis) **Radiotherapy complications (flap thinning and capsular contracture)**
Pinell-White 2015	C, M, R	97 (102)	Patients who underwent mastectomy, autologous or prosthetic reconstruction and had postoperative breast imaging at single hospital	Those who underwent AFG as an adjunct to breast reconstruction. Reason for AFG treatment not reported (e.g. pain or suboptimal outcomes)	Those who did not receive AFG, matched for various variables. Unclear if did not require or did not want AFG	Low	Abnormal breast imaging and biopsy due to AFG complications (fat necrosis, scarring, and calcification)
Weichman 2013	C, NM, R	374	Patients undergoing autologous breast reconstruction with microvascular free flaps, with or without radiation	Secondary AFG to augment volume-deficient reconstructions and need to improve postoperative contour abnormalities	No secondary AFG. Unclear if did not require or did not want AFG	Medium-high	Surgical characteristics of patients who did and did not require AFG. Surgical complications and revisions
Subpopulation: A3							
Khan 2017	C, NM, R	71	Patients with early breast cancer who underwent BCS and whole breast radiotherapy	Immediate AFG after BCS	BCS alone	Low-medium	Locoregional recurrence **% of patients satisfied/dissatisfied by each of the BREAST-Q domains**
Mestak 2016	C, M, R	77	Patients who underwent BCS with radiotherapy	Breast reconstruction using AFG alone	Those who did not have AFG (with or without other reconstruction), matched for	Low	Locoregional recurrence

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Author	Design	N[a]	Population detail	Intervention group	Comparator group	Risk of bias[b]	Outcomes[c]
					various variables. Unclear if did not require or did not want AFG		
Stumpf 2017	C, NM, R	194	Patients with invasive breast cancer submitted to BCS, most receiving radiotherapy	Patients undergoing BCS with immediate AFG (2010-2011)	Patients undergoing BCS without breast reconstruction (2004-2009)	High	Locoregional recurrence

Abbreviations: AFG = autologous fat graft; BCS = breast conserving surgery; BSC = best supportive care; C = comparative study; NM = not matched; NRS = numerical rating scale; PMPS = post mastectomy pain syndrome; R = retrospective; RCT = randomised controlled trial

[a] number of patients (breasts);

[b] RCTs assessed by Cochrane tool for assessing risk of bias of RCTs, comparative studies by ROBINS-I

[c] outcomes in bold typography were used in the economic evaluation

Source: Table 22, p99; Table 25, p106; Table 30, p112; Table 39, p128; Table 41, p130 of the DCAR.

Table 4 Summary of the evidence available for Population B

Author	Design	N[a]	Population detail	Intervention group	Comparator group	Risk of bias[b]	Outcomes
Brault 2017	C, NM, R	37 (63)	Patients with grade I to III (Groleau scale) tuberous breast deformities, with no associated breast disease (breast cancer or other syndromes)	Exclusively treated with AFG	Corrective breast surgery (exclusively treated with prostheses)	High	Patient satisfaction BREAST-Q Complications
Tenna 2017	C, NM, R	46 (88)	Patients who underwent correction of a tuberous breast deformity	AFG as a secondary procedure in implant or autologous reconstructions	AFG as a primary procedure (in conjunction with rigottomies)	High	

Abbreviations: AFG = autologous fat graft; C = comparative study; NM = not matched; R = retrospective

[a] number of patients (breasts)

[b] RCTs assessed by Cochrane tool for assessing risk of bias of RCTs, comparative studies by ROBINS-I

Source: Table 41, p130 of the DCAR.

The pre-ESC response stated that the literature cited in the DCAR is inadequate in regard to the effect of mastectomy on women and the health benefits of breast reconstruction. The applicant also claimed that the DCAR inappropriately focussed only on post-mastectomy pain syndrome and "aesthetics" as improvable domains for these women. There is no mention of psychosocial or physical benefits of breast reconstruction, for which the applicant claimed there is ample evidence in both the international and Australian literature.

In the rejoinder, the assessment group noted pain relief was nominated as an outcome for Population A, while neither depression nor self-esteem were mentioned as a separate outcome. Disease-specific quality of life (QoL) was captured with the validated instrument BREAST-Q, which included psychological and physical wellbeing. BREAST-Q outcomes in every study that met the inclusion criteria were duly extracted and reported.

Population A

Post mastectomy pain syndrome (PMPS) subpopulation
The DCAR stated that other than stating 'no complications of the fat grafting were observed' (but no description of what 'complications' explicitly included, and no discussion of complications in the comparator arm), Juhl (2016) included no safety outcome data. Caviggioli (2011)[7], Caviggioli (2016)[8] and Maione (2014)[9] reported no safety data.

Subpopulation A1: Post mastectomy without reconstruction
The DCAR stated that Calabrese (2018) reported locoregional and systemic recurrence, reporting no statistically significant differences among patients who underwent nipple sparing mastectomy (NSM) and breast reconstruction with a tissue expander (TE) temporary breast prosthesis who were treated with AFG (stromal vascular fraction (SVF)-enriched or standard (Coleman procedure)) *vs.* those who were not. Ribuffo (2013)[10] reported on patients who had undergone a modified radical mastectomy (MRM) with immediate two-stage prosthetic reconstruction using post mastectomy radiation therapy (PMRT) with AFG on irradiated breast expanders compared with those who underwent PMRT without AFG; statistically significantly fewer patients treated with AFG exhibited any short- or long-term complication such as infection, extrusion, or radiodermitis sequelae.

Subpopulation A2: Post mastectomy with reconstruction
The DCAR stated that four studies reported recurrence among those treated with AFG or not after total mastectomy and delayed deep inferior epigastric perforator (DIEP)-flap reconstruction (Fertsch 2017[11], Laporta 2015[12]); secondary revision surgery, after autologous- or prosthesis-based (immediate or delayed) reconstruction (Kim 2014[13]) or reconstruction with free flaps (DIEP, superficial inferior epigastric artery [SIEA], superior gluteal artery perforator [SGAP], inferior gluteal artery perforator [IGAP] and thoracodorsal

[7] Caviggioli F, Maione L, Forcellini D, Klinger F, Klinger M (2011) Plastic and reconstructive surgery. 128(2):349-52.

[8] Caviggioli F, Maione L, Klinger F, Lisa A, Klinger M (2016) Stem Cells International.

[9] Maione L, Vinci V, Caviggioli F, Klinger F, Banzatti B, Catania B, et al. (2014) Aesthetic plastic surgery. 38(3):528-32.

[10] Ribuffo D, Atzeni M, Guerra M, Bucher S, Politi C, Deidda M, et al. (2013) Aesthetic Plastic Surgery. 37(6):1146-52.

[11] Fertsch S, Hagouan M, Munder B, Schulz T, Abu-Ghazaleh A, Schaberick J, et al. (2017) Gland Surgery. 6(4):315-23.

[12] Laporta R, Longo B, Sorotos M, Pagnoni M, Santanelli di Pompeo F (2015) Aesthetic plastic surgery. 39(3):339-49.

[13] Kim HY, Jung BK, Lew DH, Lee DW (2014) Archives of Plastic Surgery. 41(6):740-7.

artery perforator [Tap]) (Masia 2015[14]). No statistically significant differences were observed in those treated with AFG or not; however, Fertsch (2017) reported statistically significantly increased recurrence among those with high-grade neoplasia or positive nodes treated with AFG during exploratory subgroup analyses.

The DCAR stated that Panettiere (2009)[15] reported that among irradiated breasts that had undergone prosthetic reconstruction, two cases of severely thinned flaps in the control group resulted in implant exposure and subsequent removal, whereas all four cases of severely thinned flaps in those treated with AFG improved following AFG, with no implant exposure (p=0.067).

The DCAR stated that Pinell-White (2015)[16] reported on patients who had undergone AFG as an adjunct to post mastectomy breast reconstruction and who also had imaging conducted at a single centre. Controls were matched for age at initial reconstruction (±5 years), year of initial reconstruction (±2 years), and type of reconstruction. Patients treated with AFG had a greater number of mammograms, ultrasounds and magnetic resonance imaging (MRI) scans, whereas the group not treated with AFG had a greater number of chest computed tomography (CT) / positron emission tomography (PET) scans; only the number mammograms reached statistical significance.

Subpopulation A3: Breast Conserving Surgery (BCS)
The DCAR stated that all studies reported recurrence (specifically local recurrence in Khan (2017)[17] and Stumpf (2017)[18]), and no differences between treatment groups was observed.

Extended harms assessment – incidence of locoregional occurrence
As part of the extended harms safety assessment, the DCAR reviewed a further 11 comparative studies[19] and one systematic review (Krastev 2018b)[20] that reported and analysed the incidence of locoregional recurrence in women with breast cancer who received AFG in multiple subgroups of Population A.

The DCAR stated that most studies and subgroup analyses indicated there were no statistically significant differences between the intervention and control groups for the incidence of locoregional recurrence. An exception to this was Petit (2012)[21] and Petit (2013)[22] observed a statistically significantly increased incidence of locoregional recurrence for those treated with AFG in subgroups defined as those: with of ductal and lobular intraepithelial neoplasia (DIN + LIN); age <50 years; Grade 3 cancer; Ki-67 ≥14%; or quadrantectomy (BCS). Petit (2013) conceded that their inclusion criteria may have reduced

[14] Masia J, Bordoni D, Pons G, Liuzza C, Castagnetti F, Falco G (2015) European journal of surgical oncology. 41(5):612-6.
[15] Panettiere P, Marchetti L, Accorsi D (2009) Aesthetic Plastic Surgery. 33(5):695-700.
[16] Pinell-White XA, Etra J, Newell M, Tuscano D, Shin K, Losken A (2015) Breast Journal. 21(5):520-5.
[17] Khan LR, Raine CR, Dixon JM (2017) European Journal of Surgical Oncology. 43(8):1402-8.
[18] Stumpf CC, Biazus JV, Zucatto F, Cericatto R, Cavalheiro JAC, Damin APS, et al. (2017) Revista do Colegio Brasileiro de Cirurgioes. 44(2):179-86.
[19] Cohen 2017, Gale 2015, Krastev 2018, Kronowitz 2016, Mazur 2018, Petit 2012, 2013 and 2017, Seth 2012, Silva-Vergara 2017, Sorrentino 2019
[20] Krastev TK, Schop SJ, Hommes J, Piatkowski AA, Heuts EM, van der Hulst RRWJ (2018b) The British Journal of Surgery. 105(9):1082-97.
[21] Petit JY, Botteri E, Lohsiriwat V, Rietjens M, De lorenzi F, Garusi C, et al. (2012) Annals of Oncology. 23(3):582-8.
[22] Petit JY, Rietjens M, Botteri E, Rotmensz N, Bertolini F, Curigliano G, et al. (2013) Annals of Oncology. 24(6):1479-84.

the expected incidence of locoregional recurrence in the control group. Kronowitz (2016)[23] also indicated that AFG was associated with an increased risk of locoregional recurrence in patients treated with hormonal therapy, 1.4% and 0.5% for the intervention and control groups, respectively (p=0.038). This remained significant when adjusted for chemotherapy, radiation therapy, and clinical stage (p=0.031).

Based on the evidence available, the DCAR considered that there are no signals of a difference in locoregional recurrence among those treated with AFG (with the exception of a small number of subgroups). The DCAR acknowledged that this conclusion is heavily reliant on largely retrospective clinical data (with differences in patient populations, length of follow-up and timing of AFG post initial surgery) and contradicts the observation in the literature in *in vitro* settings suggesting a role for fat in cancer initiation and progression.

Population B: Developmental breast abnormalities

The DCAR stated that neither Brault (2017)[24] nor Tenna (2017)[25] reported on any safety outcomes other than those described for secondary procedures below.

11.   Comparative effectiveness

Population A

Post mastectomy pain syndrome (PMPS) subpopulation
The DCAR stated that Juhl (2016) reported statistically significant improvements for pain outcomes in the AFG-treated group were observed between baseline and 6 months. Each comparative study similarly reported statistically significant improvements in pain outcomes from baseline to final follow-up in those treated with AFG. Juhl (2016) reported statistically significant differences between groups in *post-hoc* analyses; Caviggioli (2016) and Maione (2014) also reported statistically significant differences between cases and controls at follow-up. Caviggioli (2011, 2016) additionally reported that 28 of 34 mastectomy patients and Caviggioli (2016) further reported 20 of 25 quadrantectomy patients ceased pharmacological therapy; the mean and median pain reduction scores were higher among those who ceased pharmacological therapy.

Subpopulation A1: Post mastectomy without reconstruction
The DCAR stated that Cuomo (2014) compared the use of AFG in conjunction with prosthesis or prosthesis alone for reconstruction in patients who underwent radical mastectomy without axillary dissection for the treatment of breast cancer; indicating that treatment with AFG during prosthetic reconstruction could reduce post-operative and subsequent pain. Ribuffo (2013) further reported that patients treated with AFG were more likely to evaluate shape/symmetry as 'good'; although not reported by the authors, this was statistically significantly different between groups (relative risk = 7.00; 95% confidence interval: 2.35, 25.25).

[23] Kronowitz SJ, Mandujano CC, Liu J, Kuerer HM, Smith B, Garvey P, et al. Plastic and reconstructive surgery. 137(2):385-93.
[24] Brault N, Stivala A, Guillier D, Moris V, Revol M, Francois C, et al. (2017) Journal of Plastic, Reconstructive & Aesthetic Surgery. 70(5):585-95.
[25] Tenna S, Cagli B, Brunetti B, Barone M, Persichetti P (2017) Aesthetic Plast Surg. 41(6):1249-58.

Subpopulation A2: Post mastectomy with reconstruction
The DCAR stated that Cogliandro (2017) reported on a group of patients who were admitted to undergo definitive prosthesis-based breast reconstruction and developed some asymmetry resulting in patients' dissatisfaction with the aesthetic outcome; all patients were offered AFG and those who agreed underwent treatment with AFG almost 1 year after surgery. The authors reported a statistically significant difference in the following states of BREAST-Q, favouring the AFG treatment group: ability to wear more fitted clothing; reconstructed breast softness; breasts of equal size relative to one another; reconstructed breast look and touch; amount of implant rippling (wrinkling) perceived by patients; psychosocial well-being and physical well-being, chest, and upper body. Similarly, Leuzzi (2019)[26] reported statistically significantly higher scores for the 'sexual well-being' domain and a number of specific BREAST-Q questions among those who underwent reconstruction with a latissimus dorsi (LD) flap with AFG compared with those with an LD flap with a prosthesis.

Lakhiani (2014)[27] reported on patients who underwent secondary breast augmentation with AFG or implant insertion following flap reconstruction. No statistically significant differences were observed for any category (contour, volume, projection and overall aesthetic appearance, conducted by a panel) between the AFG and implant alone groups; however statistically significantly better aesthetic outcomes were reported for the AFG + implant group with respect to contour, volume and overall appearance, compared with both AFG and implant alone.

Panettiere (2009) reported that superficial irregularities among patients treated with AFG completely resolved in 11 (of 20) cases and significantly improved in the remaining nine. Panettiere (2009) also reported changes in the average aesthetic outcome (rated from 1 (very poor) to 5 (very good)) before AFG (T0) and at about three months after the last (of serial sessions repeated after a minimum of 20 days until the result was stable or the patient was satisfied) session of AFG (T1) in the intervention group. Mean (SD) aesthetic score was similar between the AFG group at T0 (2.7 (0.8)) compared with the no AFG group (3.1 (1.6)), $p \leq 0.18$; and significantly improved in the intervention arm at T1 (4.3 (0.6)) compared with T0 (2.7 (0.8)), $p \leq 0.001$. The outcomes for the control group at T1 were not reported, suggesting a possible overestimate of the gain in the aesthetic scores in the intervention group.

Conversely, Laporta (2015) reported no statistically difference between those treated with AFG or not from the results of patient and surgeon (two independent observers, blinded to treatment group) surveys.

Subpopulation A3: Breast Conserving Surgery (BCS)
The DCAR stated that Khan (2017) additionally reported results from BREAST-Q, indicating that statistically significant differences, favouring the intervention group, were observed for the following (i) appearance in the mirror clothed and unclothed; (ii) shape of breasts in bra; (iii) size of breasts; (iv) ability to wear fitted clothing; (v) equality of size of breasts; and (vi) how closely matched the breasts are to each other. The AFG group was statistically significantly more satisfied with overall cosmetic outcomes compared with the no AFG group.

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[26] Leuzzi S, Stivala A, Shaff JB, Maroccia A, Rausky J, Revol M, et al. (2019) Journal of Plastic, Reconstructive and Aesthetic Surgery. 72(3):381-93.
[27] Lakhiani C, Hammoudeh ZS, Aho JM, Lee M, Rasko Y, Cheng A, et al. (2014) European Journal of Plastic Surgery. 37(11):609-18.

Population B: Developmental breast abnormalities

The DCAR stated that for patients undergoing breast augmentation with implant alone in Brault (2017), they were statistically significantly more satisfied with their breasts and their outcome compared with those undergoing augmentation with AFG alone. Brault (2017) provided further results question by question, reporting that statistically significant differences between groups, in favour of implant alone, were observed for most questions (9/13) in the "satisfaction of breast section". However, patients treated with AFG alone had statistically significant higher scores for "how your scars look". Similarly, the implant alone group had statistically significantly higher score for six of eight questions in the "satisfaction with outcome" module. Tenna (2017) reported that secondary procedures were required in 28.5% (largely due to dissatisfaction) and 63.5% (largely due to major and minor complications); and the mean number of procedures was 1.28 and 1.96, in the autologous group and implant groups, respectively. Based on BREAST-Q scores in Tenna (2017), patient satisfaction was comparable between the intervention and comparator groups across all domains (p values were not reported, but what appear to be standard deviations around the mean values indicate statistically significant differences were unlikely).

Summary

The DCARs resulting clinical conclusions regarding the comparative safety and effectiveness of AFG *vs.* no AFG (BSC) and AFG *vs.* reconstruction are summarised in **Table 5** and **Table 6**, respectively. Note, the DCAR did not include all identified studies within **Table 5** and **Table 6** due to (i) not reporting results for the various outcomes, or (ii) not providing results of a comparison of AFG *vs.* no AFG.

Table 5 Summary of the evidence and clinical claims for AFG vs. no AFG (BSC) (number of studies; number of patients)

Outcome	Population A1	A2	A3	B
Locoregional recurrence	↔ (1; 169)[a] ⊕⊙⊙⊙	↔ (4; 998)[b] ⊕⊕⊙⊙	↔ (3; 342) ⊕⊕⊙⊙	NA
Distant or systemic recurrence	↔ (1; 169)[a] ⊕⊙⊙⊙	NR	↔ (1; 194) ⊕⊙⊙⊙	NA
Reconstruction complications	↓ (1; 32)[a] ⊕⊙⊙⊙	↓ (2; 131) ⊕⊙⊙⊙	NR	NR
Other complications	↔ (2; 85)[a] ⊕⊙⊙⊙	↔ (1; 70) ⊕⊙⊙⊙	NR	NR
Radiological abnormalities	NR	↔ (1; 97) ⊕⊕⊙⊙	NR	NR
Safety	**Uncertain**	**Uncertain**	**Uncertain**	**Not informed**
PMPS	↓ (1; 15)[c] ⊕⊙⊙⊙	↓ (1; 113)[d] ⊕⊙⊙⊙	↓ (1; 96)[d] ⊕⊙⊙⊙	NA
Pain (e.g. post-operative)	↓ (1; 55)[a] ⊕⊙⊙⊙	NR	NR	NA
HRQoL (BREAST-Q)	NR	↑ (1; 70) ⊕⊙⊙⊙	↑ (1; 71) ⊕⊙⊙⊙	NR
Patient and surgeon satisfaction	NR	↔ (1; 40) ⊕⊙⊙⊙	NR	NR
Aesthetics	↑ (1; 32)[a] ⊕⊙⊙⊙	↑ (1; 7)[e] ⊕⊙⊙⊙	NR	NR
Effect	**Superior**	**Superior**	**Superior**	**Not informed**

AFG = autologous fat graft; BSC = best supportive care; HRQoL = health-related quality of life; NA = not applicable; NR = not reported; PMPS = post mastectomy pain syndrome

↔   no statistically significantly differences between treatment groups

↓   statistically significantly reduced in those treated with AFG

↑   statistically significantly increased in those treated with AFG

[a]   not in a strictly "no reconstruction" population; but use of AFG during (rather than after) the reconstruction process

[b]   statistically significant differences, favouring control, for some subgroups

[c]   based on *post hoc* subgroup analyses across groups for DoloTest outcomes

[d]   reduced VAS scores and analgesic use among those treated with AFG

[e]   includes only 4 (AFG + implant) and 3 (implant alone) patients, respectively, from Lakhiani 2014

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊙ **Moderate quality:** 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 quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Source: Table 3, p37 of the DCAR.

Table 6   Summary of the evidence and clinical claims for AFG vs. reconstruction alone (number of studies; number of patients)

Outcome	Population A1	A2	A3	B
Locoregional recurrence	NR	NR	NR	NA
Distant or systemic recurrence	NR	NR	NR	NA
Reconstruction complications	NR	↔ (1; 90) ⊕⊙⊙⊙	NR	↔ (1; 63 breasts)[b] ↓ (1; 46)[c] ⊕⊙⊙⊙
Other complications	NR	↔ (2; 109)[a] ⊕⊙⊙⊙	NR	NR
Radiological abnormalities	NR	NR	NR	NR
Safety	**Not informed**	**Uncertain**	**Not informed**	**Uncertain**
Pain	NR	NR	NR	NA
HRQoL (BREAST-Q)	NR	↑ (1; 90) ⊕⊙⊙⊙	NR	↓ (1; 63 breasts)[b] ↔ (1; 46)[c] ⊕⊙⊙⊙
Patient and surgeon satisfaction	NR	NR	NR	NR
Aesthetics	NR	↔ (1; 19)[a] ⊕⊙⊙⊙	NR	NR
Effect	**Not informed**	**Superior**	**Not informed**	**Uncertain**

HRQoL = health-related quality of life; NA = not applicable; NR = not reported

↔   no statistically significantly differences between treatment groups

↓   statistically significantly reduced in those treated with AFG

↑   statistically significantly increased in those treated with AFG

[a]   includes only 16 (AFG alone) and 3 (implant alone) patients, respectively, from Lakhiani 2014

[b]   uncertainty in the validity of this conclusion given a higher degree of deformity observed in the AFG group *vs.* implant group

[c]   limited applicability to an AFG-treated Subpopulation As only five of 16 patients (5 breasts) had autologous reconstruction that included AFG. Additionally, the implant group was characterised by the higher degree of deformity with 74% of breasts belonging to type III, *vs.* 26% in the autologous group

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊙ **Moderate quality:** 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 quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Source: Table 4, p39 of the DCAR.

Clinical claim

The Ratified PICO Confirmation indicated that in each of the populations, where the comparator is best supportive care (i.e. no specific intervention and the patient lives with abnormality they otherwise would like treated), the appropriate clinical claim for AFG is likely to be one of superior effectiveness and that where AFG is to be compared to alternative surgeries or repeat/revisional surgeries it was not yet possible to determine an appropriate clinical claim.

On the basis of the evidence reviewed and summarised above in **Table 5** and **Table 6** the DCAR suggested that for:
- Population A
  - relative to BSC (no AFG), AFG has uncertain safety and superior effectiveness in the treatment of PMPS in Subpopulations A1, A2 and A3
  - relative to BSC (no AFG), AFG has uncertain overall safety and superior effectiveness in Subpopulations A1, A2 and A3
  - relative to reconstruction alone, AFG has uncertain safety and superior effectiveness in Subpopulation A2.

- Population B
  - relative to reconstruction alone, AFG has uncertain comparative safety and effectiveness.

The DCAR stated that due to the absence of comparative study data, a claim could not be informed for the comparisons:
- AFG compared to reconstruction for Subpopulation A1 and A3
- AFG compared to no AFG (BSC) for Population B.

Translation issues

The DCAR stated that the targeted literature search did not identify an economic evaluation of AFG. No utility estimates associated with AFG-relevant health states in the nominated populations were found. In most cases the clinical evidence did not provide outcomes suitable for a meaningful economic evaluation. In many instances the aesthetic outcomes were expressed in point (or standardised point) differences in BREAST-Q or some other *ad hoc* scale that was not validated, which were not sufficiently informative for decision making. In other instances it was possible to construct the outcome that could be utilised in an economic evaluation, although this required transformations and, in some cases, arbitrary interpretations, which limited the usefulness of these outcomes (see subheading *Cost-effectiveness exercises: CEA*).

The DCAR indicated that the only outcome for which a conventional outcome of a "proportion of responders" was available, was reduction in pain and analgesic use among patients with PMPS in Subpopulations A2 and A3. This outcome enabled a modelled economic evaluation and a number of sensitivity analyses. The relevant translation issues were (i) estimates of overall survival (general population mortality was used in the base case and breast cancer specific mortality was used in sensitivity analysis, real estimate likely to lie somewhere between) and (ii) the intermediate outcome defined as "response" to AFG and assessed as the proportion of patients who no longer required analgesics (the benefit that was assumed to last a lifetime) was transformed into life-years free of pain (LYFP).

12. Economic evaluation

Based on the clinical evaluation, the DCAR performed:
- a trial-based and modelled economic evaluation (CEA) for the use of AFG in the treatment of PMPS in Subpopulations A2 and A3
- a series of cost-effectiveness exercises[28]:
  - trial based analyses (CEA) for a reduction in reconstruction complications for Subpopulations A1 and A2 (AFG *vs.* no AFG)
  - trial based analyses (CEA) for increased satisfaction with outcome assessed by various measures in Subpopulations A2 (AFG *vs.* no AFG and AFG *vs.* implant) and Subpopulation A3 (AFG *vs.* no AFG)

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[28] The DCAR stated that the term "exercise" is used here in order not to confuse the following with the full-scale economic evaluations. All analyses were conducted from the Australian Health Care System perspective. In many instances in order to derive a result (incremental cost-effectiveness ratio; ICER) a number of assumptions had to be made, that are likely to compromise the validity of results. In these populations, poor quality and inadequate reporting of the limited evidence made it impossible to assess the degree and the direction of bias of the results. The results should be interpreted with caution.

o   a cost-minimisation analysis (CMA) was conducted for AFG *vs.* reconstruction alone in Population B.

Population A

Trial-based economic evaluation - PMPS

The DCAR conducted a trial-based economic evaluation over 12 months (**Table 7**) using the comparative studies by Caviggioli (2011, 2016), which were conducted in a small cohort of irradiated post mastectomy and post lumpectomy populations who met the criteria for PMPS. The DCAR noted that demographic and other patient characteristics were not reported in Caviggioli (2011, 2016).

Table 7 Summary of the trial-based economic evaluation for PMPS (Subpopulations A2 and A3)

Perspective	Australian Health Care System
Comparator	Best supportive care (pregabalin 300mg daily)
Type of economic evaluation	Cost-effectiveness
Sources of evidence	Systematic review (Section B-PMPS); Comparative studies (Caviggioli 2011, 2016)
Time horizon	12 months
Outcomes	Proportion of responders
Methods used to generate results	Comparative studies (Caviggioli 2011, 2016)
Health states	Not applicable
Cycle length	Not applicable
Discount rate	Not applicable
Software packages used	Not applicable (simple arithmetical calculation)

Abbreviations: PMPS = post mastectomy pain syndrome
Source: Table 56, p156 of the DCAR.

A cost per responder (defined as the proportion who ceased analgesics) of $1,076.82 was estimated (**Table 8**).

Table 8   Summary of trial-based economic evaluation for PMPS

Alternative strategies	Cost	Incremental cost	Effectiveness (response)	Incremental effectiveness	ICER
AFG	$1,049	$872	81%	81%	$1,076
Best supportive care	$177		0		per responder

Abbreviations: AFG=autologous fat grafting; ICER = incremental cost effectiveness ratio; PMPS= post mastectomy pain syndrome

Modelled economic evaluation – PMPS

In addition, the DCAR presented a modelled CEA, which extends the model to a lifetime is summarised in **Table 9**.

Table 9   Summary of the economic evaluation for PMPS (Subpopulations A2 and A3)

Perspective	Australian Health Care System
Comparator	Best supportive care (pregabalin 300mg daily)
Type of economic evaluation	Cost-effectiveness
Sources of evidence	Systematic review (Section B-PMPS); Comparative studies (Caviggioli 2011, 2016)
Time horizon	Lifetime (40 years from the starting age of 60 years)
Outcomes	Life-year free of PMPS
Methods used to generate results	Comparative studies (Caviggioli 2011, 2016)
Health states	"responder"; "non-responder"; alive - free of pain; alive with PMPS; dead
Cycle length	A year
Discount rate	5%
Software packages used	TreeAge Pro 2019 R2.1

Abbreviation: PMPS = post mastectomy pain syndrome
Source: Table 5, p40 of the DCAR.

The key structural assumption of the model was that a response rate (81%[29] of patients who no longer took analgesics; applicable to both Subpopulations A2 and A3) observed in the subgroup of patients who took analgesics at baseline was applied to the rest of the cohort. In the base case analysis, the age of PMPS patients receiving AFG treatment was conservatively assumed at 60 years old, consistent with the population in the RCT (Juhl 2016). The health gain associated with a reduction in pain (i.e. becoming a "responder") was assumed to last a lifetime until a patient reached 100 years of age. Benefits, expressed in terms of life-year free of pain (LYFP), were accumulated over 40 years until most of the cohort (96.5%) are dead of natural causes.

Table 10 shows the base case analysis results for use of AFG for treatment of PMPS in Subpopulations A2 and A3.

Table 10 Base case analysis results of the economic evaluation in the irradiated post mastectomy and post lumpectomy population with PMPS

Alternative strategies	Cost	Incremental cost	Effectiveness (LYFP)	Incremental effectiveness	ICER
AFG	$1,482.35[a]	-$1,062.48	22.17	22.17	AFG dominates
Best supportive care	$2,544.82[a]		0		

Abbreviations: AFG=autologous fat grafting; LYFP = life year free of pain; ICER = incremental cost effectiveness ratio; PMPS= post mastectomy pain syndrome
[a]   The cost results are expressed in terms of the accumulated cost per patient in each arm over 40 years and therefore are not the same as the cost of a single AFG procedure or the annual (weighted) cost of analgesics
Source: Table 6, p42 of the DCAR.

The DCAR stated that the 12 month incremental cost of $1,076.82 per additional responder was more than offset by the ongoing cost of analgesic use (pregabalin, 300 mg/day) by 100% of patients in the comparator (BSC) arm *vs.* 19% of patients in the AFG arm (of the 44% assumed to have been taking analgesics at baseline in each arm). The incremental lifetime gain was estimated at 22.17 LYFP; the lifetime (40 years in the base case) savings were

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[29] The average of the proportions in 28/34 (82%) patients who no longer took analgesics in Caviggioli (2011) and 20/25 (80%) patients in Caviggioli (2016)

$1,062.48. AFG was found to dominate the comparator, BSC. However, the DCAR stated that this conclusion is conditional on multiple assumptions made for the model, notably the lifetime duration of benefit, which together with the high risk of bias in the two small-size comparative studies (Caviggioli 2011, 2016) produced highly uncertain results. The DCAR stated that the results of the model were most sensitive to the variation in mortality rates, starting age of patients, proportion of responders and the cost of analgesics, however AFG remained dominant in all sensitivity analyses.

The DCAR stated that on the basis of the limited data, there are no reliable estimates of the benefit in terms of LYFP and the potential cost-savings to the health system. In particular, there was no evidence to assess how bilateral *vs.* unilateral AFG would affect the costs and estimates of LYFP. Also, in the absence of long-term data on the longevity of the AFG effect on PMPS pain, the results may favour AFG over BSC. Therefore, results of the modelled economic evaluation should be interpreted with caution.

Cost-effectiveness exercises: CEA
A series of trial-based cost-effectiveness exercises (see **Table 11** below) were conducted by the DCAR on the following outcomes and in the following populations: (i) reduction in reconstruction complications (Subpopulations A1 and A2); and (ii) increased satisfaction (Subpopulations A2 and A3).

Reduction in reconstruction complications
The DCAR compared AFG (as an adjuvant procedure) in post mastectomy populations with irradiated skin developed after radiotherapy either on the implant (Population A2; Panettiere 2009) or on the expander (Population A1; Ribuffo 2013) *vs.* no AFG. The DCAR noted that the cost-offsets of the AFG sessions in Ribuffo (2013) were more expensive as, unlike in the study by Panettiere (2009), they were not limited to avoiding removal and replacement of a prosthesis. In addition, with the difference in the mean number of AFG sessions (1.4 *vs.* 3.4 in Ribuffo 2013 and Panettiere 2009, respectively), the incremental cost-effectiveness ratio (ICER) of $776 for one additional reconstruction failure avoided in Ribuffo (2013) was significantly lower than $30,469 in Panettiere (2009).

Increased satisfaction
Based on Lakhiani (2014), AFG alone was less costly and more effective and AFG plus implant was more expensive and more effective, than implant alone. However, the DCAR did not provide ICER for the outcomes based on aesthetic outcomes expressed in points on a scale of unknown validity. Based on Leuzzi (2019), AFG alone is a dominant strategy in comparison to implant ± AFG as an adjuvant procedure.

Based on Khan (2017), which assessed the degree of satisfaction with AFG as a secondary surgery using the BREAST-Q instrument, the indicative ICER was $1,106 to $2,140 per very satisfied patient (relative to no AFG). The DCAR considered that notwithstanding the limitations of the sample size and the reporting of outcomes, it appears that there is potential for AFG to eliminate a range of breast pain and tenderness symptoms in patients who had a combination of BSC and AFG. The indicative ICER estimate is $6,739 per additional patient free from symptoms. However, it was noted that AFG intervention in (Khan 2017) was used immediately (rather than delayed AFG as per proposed intervention), and thus would have applicability concerns.

Comparator	Source of evidence	Assessment method	Incremental cost ($)	Incremental effectiveness	ICER	Comments
No AFG	Panettiere 2009 (A2) Ribuffo 2013 (A1)	Events. Reduction in risk of radiation-induced complications: implant exposure, ulcerations and capsular contracture	2,132 335	-0.07 -0.44	$30,469 $776 per reconstruction failure avoided	Particularly poor reporting. Small samples in both studies. The ICER estimates the incremental cost per "reconstruction failure avoided". Unclear how the control group was selected in Ribuffo (2013)
a) Implant alone Implant ± AFG	Lakhiani 2014; Leuzzi 2019	5-point aesthetic assessment by surgeons using photographs BREAST-Q points (in SD)	-315 752 -1,481	0.2 points 0.9 points 13 SDa (standardised point difference)	Not calculated AFG alone dominates Implant ± AFG	Small size implant groups (5 breasts in AFG + implant; 8 breasts in implant only arm), no patient-reported outcomes. Difference of a fraction of a point is not informative for the ICER estimate. Not clear if the unit of reporting was a breast or a patient. Results for AFG + implant arm were not reported separately from AFG only
No AFG, BCS alone	Khan 2017	Percentage of patients who are a)"very satisfied" with BREAST-Q appearance items (cosmetic outcomes); b) patients who experienced at least one of the symptoms (pain, tenderness etc.)	321	a) 15% to 29% b) -4.7%	a) $1,106 to $2,140 per % very satisfied patients. b) $6,739	The AFG intervention is outside the DCAR scope (immediate rather than delayed AFG). Specifically targeted a subgroup of patients who had large cancers or limited breast volumes. Control group was not meant to match the intervention group

ast conserving surgery; ICER = incremental cost-effectiveness ratio; LD = latissimus dorsi; RT = radiotherapy; SD = standard deviation
original measurement points. The SD unit directly depicts the degree of normality or abnormality of a value because it expresses the deviation of an individual

Population B

Cost-effectiveness exercise: CMA
The results of the DCARs cost-minimisation analyses for Population B are shown in **Table 12** (based on Tenna 2017) and **Table 13** (based on Brault 2017). The DCAR noted that the included studies consisted of a small sample of patients with tuberous breast deformity (TBD) corrected with AFG as a primary procedure.

Table 12 Results of the cost-minimisation analysis of the alternative strategies after Tenna (2017)

Primary surgical procedure	Cost per TBD breast (primary surgery)	Cost per TBD breast (secondary surgery)	Cost per TBD breast (primary and secondary surgeries)	Incremental cost per TBD breast *vs.* AFG
AFG	$642	$233	$875	-
Autologous	$994	$233	$1,227	-$352
Implant	$1,295	$542	$1,837	-$962

Abbreviations: TBD = tuberous breast deformity
Source: Table 76, p 186 of the DCAR.

Based on the data reported in Tenna (2017), AFG is the least costly option when compared with autologous procedures and implant-based corrections of TBD.

Table 13 Results of the illustrative cost-minimisation analysis of the alternative strategies after Brault (2017)

Primary surgical procedure	Cost per TBD breast (primary surgery)	Cost per TBD breast (secondary surgery)	Cost per TBD breast (primary and secondary surgeries)	Incremental cost per TBD breast *vs.* AFG
AFG	$547	$1,108	$1,654	-
Implant	$977	$1,093	$2,070	-$416

Abbreviations: TBD = tuberous breast deformity
Source: Table 77, p186 of the DCAR.

Consistent with Tenna (2017), a comparison based on Brault (2017) indicated that AFG as a primary surgery is cost-minimising when compared with implant-based correction of TBD. However, the DCAR considered that results should be interpreted with caution as they are based on a small sample of patients with TBD breasts, incomplete reporting (e.g. the absence of detail about the secondary procedures in Tenna 2017 and the lack of clarity about the unit of measurement [per person *vs.* per breast] in Brault 2017) and the assumption that MBS items would sufficiently represent the total cost from healthcare system perspective, which may bias the results with unknown direction.

13. Financial/budgetary impacts

The DCAR used an epidemiological approach to estimate the financial implications of the introduction of AFG (**Table 14**). The DCAR stated that estimates for the PMPS subpopulation include those who may or may not proceed to reconstruction. Estimates for Subpopulations A1-A3 are assumed to not include patients with PMPS.

The DCAR estimated that the listing of AFG may result in 6,004 MBS-funded AFG services in Year 1, increasing to 7,557 in Year 5. The cost to the MBS, after co-payments have been accounted for is estimated to be $3.6M in Year 1 increasing to $4.4M in Year 5.

Table 14 Total services and costs to the MBS associated with AFG (after co-payments)

Variable	2020-21 Year 1	2021-22 Year 2	2022-23 Year 3	2023-24 Year 4	2024-25 Year 5
Population A					
PMPS subpopulation					
Number of services	1585	1939	2138	2364	2842
Total Cost to MBS	$983,055	$1,153,284	$1,249,252	$1,357,902	$1,588,054
Subpopulation A1					
Total services	1093	1093	1093	1093	1093
Total cost to MBS	$685,642	$685,642	$685,642	$685,642	$685,642
Subpopulation A2					
Number of services	967	967	967	967	967
Total cost to MBS after co-pay	$607,649	$607,649	$607,649	$607,649	$607,649
Subpopulation A3					
Number of services	2150	2215	2281	2349	2420
Total cost to MBS after co-pay	$1,333,416	$1,373,418	$1,414,621	$1,457,059	$1,500,771
Total services – Population A	5795	6214	6479	6773	7322
Total cost to MBS - Population A	$3,609,762	$3,819,993	$3,957,164	$4,108,252	$4,382,116
Population B					
Number of services	209	215	222	228	235
Total cost to MBS	$24,819	$25,564	$26,331	$27,120	$27,934
Totals for Population A+B					
Total services	**6004**	**6429**	**6701**	**7001**	**7557**
Total costs	**$3,634,581**	**$3,845,557**	**$3,983,495**	**$4,135,372**	**$4,410,050**

Source: Table 98, p216 of the DCAR.

For implications to other Government Budgets, the DCAR estimated that there are likely to be cost savings to the PBS from the reduction in the use of analgesia for long-term chronic pain specific to the PMPS subpopulation. The DCAR assumed pregabalin 300 mg/day would be the recommended pain treatment regimen (first-line) as it was the predominate use analgesic in the systematic review and meta-analyses by Finnerup (2015) and Tait (2018). However, the DACR noted combination therapies (i.e. other anti-depressants, opioids) were also used and excluding these costs may underestimate the substitution of AFG for analgesia. The DCAR noted assuming 300 mg of pregabalin a day, savings to the PBS were assessed as $525K in Year 1 increasing to $942K in Year 5 after co-payments are accounted for (**Table 15**).

Table 15 Implications for other government budgets (PBS) for PMPS subpopulation

Variable		2020-21 Year 1	2021-22 Year 2	2022-23 Year 3	2023-24 Year 4	2024-25 Year 5
Prevalence	A	71,943	71,943	71,943	71,943	71,943
Incidence	B	19,371	19,371	19,371	19,371	19,371
% who have BCS	C	45%				
% who have total mastectomy	D	55%				
Number treated with AFG	E	1585	1939	2138	2364	2842
Yearly costs for pregabalin 300mg	F; $0.89/day	$326.02	$326.02	$326.02	$326.02	$326.02
Proportion both pops cease analgesia after AFG	G	81%				
Number cease analgesia	H=E*G	1284	1570	1732	1915	2302
Drug savings 300mg	I=F*H	($418,598)	($511,982)	($564,628)	($624,231)	($750,487)
Saving after co-pay 300mg	$0.17/day	($355,808)	($435,185)	($479,934)	($530,596)	($637,914)
Pain specialist MBS item 2801	155.60 ($132.30)	($169,815)	($207,699)	($229,056)	($253,236)	($304,455)
Total savings		**($525,624)**	**($642,884)**	**($708,990)**	**($783,832)**	**($942,369)**

AFG = autologous fat graft; BCS = breast conserving surgery
Values in brackets and red text represent savings

For all other AFG subpopulations (A1, A2, A3) and Population B, the DCAR assumed there is not to be any implications for government health budgets if AFG is listed.

Overall, the DCAR considered there is considerable uncertainty in the financial estimates:
- The DCAR was unable to identify studies, with the exception of pain studies, that provided clinical evidence of the substitution of AFG for current procedures. Most studies that had a current surgical option as a comparator also included AFG for secondary usage. It was unclear whether utilisation and costs would be over or underestimated.
- In estimating the usage of AFG, the number of procedures used to calculate the cost of AFG has mainly been from clinical studies where available. The number of AFG procedures is conservative when compared to the requested number of sessions in the ratified PICO Confirmation and may not reflect likely usage in Australia, which might result in the utilisation and costs to be underestimated.
- For most of the populations, it was not possible to estimate a prevalent population. There is potentially a large pool of patients who are post mastectomy or have had a reconstruction for which AFG may provide a service. Consequently, the utilisation and costs may have been underestimated.
- The ability of AFG to substitute or be an adjunct for current services will be individual to each patient. The type and extensiveness of the breast reconstruction will be determined by the surgeon based on the extensiveness of the surgical and radiological treatment for the breast cancer, time between treatment for breast cancer and breast reconstruction, the presence and extensiveness of any prior breast reconstruction, the type of poor outcomes or the severity of the developmental breast condition. In addition, other factors such as age and any co-morbid conditions (such as diabetes) will impact on the surgical choices made. These individual characteristics could not be captured in the population and service estimates.

The pre-ESC response claimed the estimated number of AFG services (6,004 in Year 1 increasing to 7,557 in Year 5) *"seems greatly overexaggerated. I would estimate a small fraction of this service volume, and recommend further discussion on this critical point"*.

In the Rejoinder, the assessment group acknowledged that due to issues with coding of breast reconstruction procedures for both MBS and AIHW data cubes, and the failure of the codes to reflect current surgical practice, the estimates were uncertain.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Low quality evidence	Most studies were low quality and had a high risk of bias, but ESC acknowledged the difficulty in conducting a study in this patient group without a risk of bias. The overall low quality evidence had flow on effects to the consideration of the economics and financials.
Uncertainty regarding clinical claims	AFG has uncertain safety in most population groups; however, noting no signal for difference in locoregional recurrence of breast cancer in Population A.
	AFG has superior effectiveness in most subgroups of Population A, noting most convincing evidence for post-mastectomy pain syndrome (PMPS) subpopulation, but much less evidence and less convincing evidence for Population B. ESC queried if different levels of evidence and outcomes in subpopulations may provide basis for restricting down this item.
Psychological benefits of AFG for women	ESC noted the applicant's pre-ESC response, which argued that the DCAR does not adequately consider the psychological benefits of AFG for women. ESC considered that long-term implications for a person's wellbeing might not be fully reflected in the available outcome measures.
Duration of treatment effect of AFG	Overall, this remained uncertain due to the limited evidence provided in the DCAR. ESC considered that more information for this could be useful for when this application is considered by MSAC.
Economic outcomes uncertain and rely heavily on assumptions	In the absence of sufficient evidence, ESC considered if a cost-consequence approach could provide a way of simplifying the problem and increasing transparency of decision making.
Financial estimates	Population A contributes most to the financial impact. ESC noted considerable uncertainties in the estimates, including issues around how breast surgery is coded through Australian Institute of Health and Welfare (AIHW) data and MBS data, uncertain extent of AFG use, and the reliance on clinical studies to inform the financial estimates. Overall, ESC considered that usage may be underestimated (as only the incident population is included, not the prevalent population) or overestimated (population estimates, and cost offsets related to analgesics from PBS).
Item descriptor - Risk of leakage	ESC noted that the risk of leakage for cosmetic purposes was greatest for Population B. ESC considered that the developmental disorders in the item descriptor should be defined (e.g. patients with congenital tuberous breasts or unilateral hypomastia causing asymmetry with a >20% difference to the contralateral side) to minimise risk of leakage.
Item descriptor - Bilateral item number	ESC advised that an item for bilateral services should also be developed to align with other MBS items.
Item descriptor - Alignment with application 1577 (AFG for the treatment of burn	ESC advised that MSAC consider aligning item descriptors for Applications 1575 and 1577; specifically, whether:

ESC key issue	ESC advice to MSAC
scars, and facial defects due to craniofacial abnormalities)	- there should be a 3-month wait between multiple services - the number of services per side should be limited to 3 or 5 - there should be a maximum lifetime limit on services.

ESC discussion

ESC noted the application was requesting Medicare Benefits Schedule (MBS) listing for autologous fat grafting (AFG) injection for the management of defects arising from breast surgery, breast cancer treatment/prevention (Population A, 3 subpopulations) and congenital breast deformity (Population B).

ESC noted this application arose from a MBS Review Taskforce recommendation and initially covered a broader population which was split into MSAC Application 1575 and 1577. The linked MSAC Application 1577 is requesting MBS listing for AFG for the treatment of burn scars, and facial defects due to craniofacial abnormalities.

In Application 1575, ESC noted that Population A is complex and heterogeneous; it includes patients who are post-mastectomy without reconstruction (A1), patients who are post-mastectomy with suboptimal outcomes following reconstruction (A2), and patients with suboptimal outcomes following breast-conserving surgery (A3). Patients can move between subgroups. ESC noted the options for management are vast and must be individualised according to patient choice, complexity of the condition and surgeon expertise. These issues make it difficult to define a true comparator for each subgroup. ESC noted in the pre-ESC response, the applicant's concern about using best supportive care (BSC) as a comparator, and in particular in Subpopulation A2 where the majority of patients would receive revisionary surgery. ESC acknowledged that BSC might not be the predominant comparator in Subpopulation A2 as advised by the applicant, but overall considered that BSC is an appropriate comparator as it was included as an option in all PICO ratified populations. In addition, ESC noted the role of patient's choice in deciding whether they have surgery or pursue non-surgical options, but BSC may be more appropriately termed 'non-surgical treatment'.

Regarding Population B, comprising patients with developmental breast abnormalities, ESC considered that the developmental disorders should be defined in the item descriptor (i.e. patients with congenital tuberous breasts or unilateral hypomastia causing asymmetry with a >20% difference to the contralateral side) to minimise the risk of leakage for cosmetic purposes.

ESC noted the proposed MBS item descriptor, which includes unilateral services only. ESC considered that an item for bilateral services should also be developed to align with other similar MBS items. ESC considered that the item descriptor should be aligned with the proposed item descriptor for MSAC Application 1577, with regards to the limit on the number of services per side (i.e. 3 or 5) and whether there should be a restriction on the time between claiming subsequent services (e.g. 3 months). ESC also noted that the item does not describe the lifetime number of sessions a patient may have, and considered this was important given that patients can have multiple indications over time.

ESC noted several safety and quality issues from a consumer perspective, including adverse events, complications with donor sites, harvesting techniques and the likelihood of the need for repeat grafts. ESC considered that these issues could be further explored.

ESC reviewed the clinical trial data, which included 35 comparative studies and 5 systematic reviews. ESC noted that most studies were low quality and had a high risk of bias (e.g. many retrospective studies, most non-matched comparative studies), but acknowledged the difficulty in conducting a study in this patient group without a risk of bias. ESC noted that the majority of the Department Contracted Assessment Report (DCAR) included evidence comparing AFG with no AFG (i.e. BSC) in Population A, but also some evidence comparing AFG with reconstruction alone in Subpopulation A2 and Population B. ESC also noted that the highest level of evidence was a single open labelled randomised controlled trial (RCT) (Juhl 2016) assessing the use of AFG in patients who were post mastectomy without reconstruction and reported on the treatment of post-mastectomy pain, which the DCAR included as an additional subpopulation of A: post-mastectomy pain syndrome (PMPS). The DCAR's rationale for this was because the comparator (BSC) is the same, regardless of where a patient may be in their reconstruction journey (defined as Subpopulations A1-A3). ESC considered this was reasonable in light of otherwise limited evidence.

Regarding comparative safety, ESC noted that there were few studies and limited reporting of safety outcomes (in particular in Population B) to inform the assessment, and many of those included showed no difference in outcomes, including rates of locoregional recurrence of breast cancer. Although exploratory subgroup analyses in one study (Fertsch 2017) showed an increase in recurrence with AFG amongst those with high grade neoplasia or positive nodes in Subpopulation A2. Overall, ESC agreed with the DCAR's clinical claim of uncertain safety of AFG *vs.* BSC or reconstruction alone in most population groups, noting that there was no conclusion for AFG *vs.* BSC in Population B, nor for AFG *vs.* reconstruction alone in Subpopulations A1 and A3.

Regarding comparative effectiveness, ESC noted that there were consistent signals that compared with the comparator, AFG resulted in reduction in pain (including PMPS assessed only in Population A), largely improved BREAST-Q scores (including up to 1 year after initial surgery; Cogliandro 2017), and improved patient satisfaction in all subgroups of Population A, where these outcomes were reported. For Population B, ESC noted there was limited and less convincing evidence that AFG improved outcomes, and that there were mixed results when assessing BREAST-Q scores for AFG *vs.* reconstruction alone. Overall, ESC agreed with the DCAR's clinical claim of superior effectiveness of AFG *vs.* BSC or reconstruction alone in most subpopulations of Population A, and uncertain effectiveness of AFG *vs.* reconstruction alone in Population B. ESC considered overall, the DCAR's evidence was strongest for showing that AFG improved PMPS in Population A. However, ESC considered that the evidence tables (see Tables 5-6) highlight the inherent bias in assessing most outcomes, further compounded by the complex patient subgroups.

ESC noted the applicant's pre-ESC response, which suggested the evidence presented in the DCAR did not adequately capture the psychological benefits for women. ESC noted that the DCAR's Rejoinder argued that disease-specific quality of life (QoL) was captured in the included studies that used the validated instrument BREAST-Q, which included psychological and physical wellbeing. ESC considered that psychological benefits are a key consideration for this application.

In addition, ESC queried whether data were available on the duration of effect of AFG in this context. The assessment group confirmed that fat can be resorbed over time, but there was little information about this in the included studies, nor sufficiently long enough evidence to assess the durability of AFG effect. ESC considered that duration of effect was an important issue and should be further explored if possible. Following the meeting, the assessment group clarified there was one relevant reference (Juhl 2016) included in the treatment of PMPS

subpopulation within the DCAR reporting 1/8 patients (12.5%) required a second treatment (outcome not reported). The DCAR had also noted that in a study by de Gast 2016, patients with neuropathic scars after cosmetic procedures, showed a peak improvement at 3 months that was sustained at 4 years. Based on the above, the DCAR had assumed that the benefit of one-off AFG intervention in responders in the economic model would last a lifetime, which was also tested through sensitivity analysis by applying 12.5% retreatment at 6 months post-initial AFG procedure. The Department noted the DCAR also cited Kim (2014) which reported a fat reabsorption rate of 32.9% [range: 25-52%] among 38 post-mastectomy patients (Subpopulation A2; pg 119 of the DCAR). The Department also noted that while there appears to be limited evidence on the duration of effect of AFG in the patient populations included in MSAC Application 1575, there is published literature on the reabsorption of AFG in a broader patient population which report a reabsorption rate that can range widely from 25 to 83% (Moustakie 2017[30]; Yu 2015[31]).

ESC considered the economic evaluation, comprising a trial-based and modelled cost-effectiveness analyses (CEA) for PMPS in Population A2+A3 and a series of 'cost-effectiveness exercises' that included trial-based CEA for Population A subpopulations and a cost-minimisation analysis for Population B. With regards to the CEA for PMPS, ESC noted that for AFG an incremental cost-effectiveness ratio (ICER) of $1,076 per responder (trial-based CEA) was derived and AFG was dominant over BSC (modelled CEA using life-years free from PMPS). ESC noted that key drivers of the modelled evaluation were the extrapolation of response and lifetime analgesic use, and that the underlying clinical evidence was assessed to have high risk of bias. ESC considered the 'cost-effectiveness exercises' were highly hypothetical and uncertain as they were based on limited clinical evidence with a high risk of bias which necessitated a number of assumptions that added further uncertainty to the underlying weak clinical evidence base. ESC noted that it was unclear how the available results would translate into incremental cost per QALY gained, and queried whether a cost–consequence analysis may be more appropriate. Overall, ESC considered that the limitations of the evidence base and the fragmentation of subpopulations present challenges in making a funding decision for a single MBS item.

ESC noted that Population A contributed most to the total cost in the budget impact. ESC also noted considerable uncertainties in the estimates, including issues around how breast surgery is coded through Australian Institute of Health and Welfare (AIHW) data and MBS data, uncertain extent of AFG use, and the reliance on clinical studies to inform the financial estimates (e.g. to estimate the number of AFG sessions). Overall, ESC considered that usage may be underestimated (as only the incident population is included, not the prevalent population) or overestimated (population estimates, and potential conservative estimation of cost offsets related to analgesics from PBS). ESC also recalled the concern raised by PASC that the incident population is estimated at around 3,000 patients per year, but the prevalent population would be much larger.

15.   Other significant factors

Nil.

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[30] Moustakie M, Papadopoulos O, Verikokos C, et al. (2017) Application of adipose-derived stromal cells in fat grafting: Basic science and literature review. Exp Ther Med. 14(3):2415-2423. doi:10.3892/etm.2017.4811
[31] Yu NZ, Huang JZ, Zhang H, et al. (2015) A systemic review of autologous fat grafting survival rate and related severe complications. Chin Med J (Engl). 128(9):1245-1251. doi:10.4103/0366-6999.156142

16.   Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

17.   Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)