



Australian Government

Department of Health

RATIFIED PICO

Application 1577:

**Autologous fat grafting (AFG) for treatment
of burn scars, and treatment of facial defects
due to craniofacial abnormalities**

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

There are two patient populations described in this document. Separate summaries of PICO criteria are provided in two tables below.

Table 1 Summary PICO criteria – POPULATION 1: Craniofacial disorders with facial asymmetry requiring reconstruction

Component	Description
Patients	<p>Craniofacial disorders with facial asymmetry (e.g. cancer surgery, other surgery, lipodystrophy-associated conditions^a, trauma), requiring reconstruction and recontouring, including:</p> <ul style="list-style-type: none"> • Congenital craniofacial syndromes • Acquired craniofacial defects
Intervention	<p>Autologous fat grafting (AFG) alone, or with other surgical procedures^b other than to the craniofacial region, to improve facial tissue deficiencies, volume differences and contour</p>
Comparator	<p>Correction of tissue deficiencies using bony reconstruction and/or free autologous flap reconstruction, in those indicated for surgery</p> <p>Usual care (e.g. psychological attendances, ophthalmology appointments, speech therapies, and other allied health services), in those not suitable for surgery or not willing to undergo invasive surgery</p>
Outcomes	<p><u>Efficacy</u></p> <ul style="list-style-type: none"> • Patient acceptance of outcome, and clinical judgement of the surgeon • Volume retention: % of volume gain relative to injected volume • Health-related quality of life <p><u>Safety</u></p> <ul style="list-style-type: none"> • Complications: <ul style="list-style-type: none"> • Donor site: <ul style="list-style-type: none"> - Local infection; - Deep vein thrombosis - Abdominal organ injury - Haematoma/bleeding - Change to skin sensation - Scarring • Reinjection site: <ul style="list-style-type: none"> - Fat necrosis - Cysts - Infection - Post-operative pain - Scarring - Contour irregularities <p><u>Economic evaluation:</u></p> <ul style="list-style-type: none"> • Number and cost of fat grafting sessions • Quality-adjusted life years (QALYs)

Component	Description
	<ul style="list-style-type: none"> • Hospital length of stay • Cost of comparator (autologous flap) operations

^a Except patients with HIV-associated lipoatrophy from antiretroviral therapy

^b Under same anaesthetic session as other surgical procedures, particularly for congenital syndromes who may have more than one site affected

Table 2 Summary PICO criteria – POPULATION 2: Burn scars

Component	Description
Patients	Burn scars ^a anywhere on the body not responding to topical and other conventional therapies and requiring treatment of dysaesthesias, contracture, poor skin quality or deformity
Intervention	AFG alone, or with other procedures, and usual care.
Comparator	Usual care (e.g. physiotherapy, pain relief, topical treatments, bandages) and/or secondary procedures (e.g. scar contracture release, repeat skin grafting or pedicle flap)
Outcomes	<p><u>Efficacy</u></p> <ul style="list-style-type: none"> • Patient acceptance of outcome, • Pain and itch relief (Patient and Observer Scar assessment Scale [POSAS]/visual analogue score [VAS]) • Restored function/mobility • Scar characteristics (assessed using POSAS) including: <ul style="list-style-type: none"> - Hardness/Thickness - Colour - Texture - Contour - Pliability - Mobility • Volume retention: % of volume gain relative to injected volume • Health-related quality of life <p><u>Safety</u></p> <ul style="list-style-type: none"> • Complications: <ul style="list-style-type: none"> • Donor site: <ul style="list-style-type: none"> - Local infection; - Deep vein thrombosis - Abdominal organ injury - Haematoma/bleeding - Change to skin sensation - Scarring • Reinjection site: <ul style="list-style-type: none"> - Fat necrosis - Cysts - Infection - Post-operative pain - Scarring - Contour irregularities

Component	Description
	<p><u>Economic evaluation:</u></p> <ul style="list-style-type: none"> • Number and cost of fat grafting sessions • Cost of secondary surgeries (when applicable) and other resources used for usual care • Cost of comparator surgeries (when applicable) • Quality-adjusted life years (QALYs) • Hospital length of stay

^a Six months after burn has healed (defined as re-epithelialisation with no ulceration)

PICO rationale for the therapeutic medical service

Population

The intervention is proposed in Australia for use in the following two distinct patient populations:

Population 1: Craniofacial disorders with facial asymmetry, requiring reconstruction and re-contouring including:

- Congenital craniofacial syndromes
- Acquired craniofacial defects (e.g. cancer surgery; other surgery; lipodystrophy-associated conditions - *except patients with HIV-associated lipodystrophy from antiretroviral therapy; trauma*)

Population 2: Burn scars not responding to topical and other conventional therapies, specifically:

- For treatment, anywhere on the body, of dysaesthesias, contracture, poor skin quality or deformity

For both populations, PASC confirmed the treatment would be applicable to both children and adults, with no age restrictions. PASC noted and accepted the two proposed populations.

These populations are discussed individually below:

Population 1: Craniofacial disorders with facial asymmetry

Craniofacial and maxillo-mandibular asymmetry and deformities have numerous aetiologies and can be congenital or acquired (through trauma, iatrogenesis, or disease).

(a) Patients with congenital craniofacial syndromes

A number of congenital craniofacial disorders, including craniosynostosis syndromes, craniofacial clefts and craniofacial macrosomia, as well as disorders such as Parry-Rhombert disease, represent a significant health burden in terms of facial expression, social ostracisation and functional problems.

These patients would need a formal diagnosis of a craniofacial disorder, being assessed by a specialist as having significant facial asymmetry or contour defect (identified through clinical evaluation by a specialist, and documented by clinical photography). Given the natural history of the condition their need for surgery changes over their lifetime.

(b) Patients with acquired craniofacial defects

From discussions with the applicant, patients who will fall within this subgroup are described as:

- patients who received treatment for craniofacial cancer—likely an older demographic of 60-75 years
- patients who received surgery for craniofacial disorders
 - patients with lipodystrophy-associated conditions, except for patients with HIV-associated lipodystrophy from antiretroviral therapy, which the applicant confirmed, based on expert advice, would not be a suitable population for the proposed intervention because other fillers are considered to be more effective and because the cohort of HIV positive patients seeking this treatment is much reduced probably due to the efficacy of modern antiretroviral drugs.
- trauma patients—likely received trauma to the facial bone, often includes facial bone fractures, emergency neurosurgery and bony reconstruction. A younger demographic of 20-40 yrs

Each of these populations will need to be clearly identified to be able to specify their current medical treatment, comparator and outcomes.

Craniofacial disorders are rare and highly heterogeneous, due to wide variations in age; underlying aetiology; and pathology. Consequently, a reliable estimate of the prevalence of patients is challenging.

The applicant has proposed that up to 100-150 patients in Australia have craniofacial defects that could be treated with AFG each year. The caseload would be largely hemifacial atrophy and more severe hemifacial macrosomia, such as Tessier clefts. There could be a small group of post traumatic facial deformities where fat grafting could be an adjunctive procedure (based on correspondence with a clinical expert).

While a back-log of patients requiring treatment is not expected, there may be a large prevalent patient population who have previously undergone substantial reconstruction who may benefit from AFG treatment (despite substantial improvement). The applicant acknowledges this historical cohort of patients may increase utilisation of AFG in the first 1-2 years, if the service is listed on the Medicare Benefits Schedule (MBS).

PASC acknowledged the possible difficulty in defining which patients with craniofacial disorders would be severe enough to qualify for AFG, if AFG were to be publicly funded. Therefore, descriptors that specify the population or give reasons for performing AFG should be considered, in order to minimise leakage. This is particularly important in the context of acquired craniofacial defects, for which there may be a broader interpretation outside the intended population.

The applicant advised that most craniofacial patients are treated in the public hospital system, meaning the number of referrals to private MBS items could be low. This means the number of services currently provided is not an accurate guide to estimate MBS utilisation. Further consultation with clinical experts is needed about estimated prevalence and incidence of craniofacial disorders in Australia, in order to clarify estimated MBS use.

Rationale

Craniofacial abnormalities negatively impact the psychological quality of life of those affected (Singh 2015; Visram 2019) and a source of severe social and aesthetic handicap (van den Eltzen 2012; Versnel 2010). Surgery to correct asymmetry in these patients has been shown to significantly improve health-related quality of life and self-esteem (Yildiz 2015).

Treatment of craniofacial abnormalities may require complex bone surgery. Despite success in achieving skeletal symmetry, noticeable facial asymmetry may persist.

AFG can be used in these patients to correct the shape and asymmetry from the underlying soft tissue deficiency without the need for tissue/flap reconstruction.

AFG is proposed to be used in **patients with craniofacial disorders with facial asymmetry requiring reconstruction and recontouring including:**

- Congenital craniofacial syndromes
- Acquired craniofacial defects

Eligibility for AFG would require patients to have a suitable donor site for fat harvest.

Population 2: Burn scars and contractures

Patients with major burns require excision of burned tissue and usually split skin grafting to reconstruct defects. Split skin grafts are thin and have no associated sub-cutaneous tissue. This results in tethering of skin to underlying muscles and fascia with associated functional problems.

In addition, split skin grafts contract and, when across joints, can limit movement. Chronic neuropathic pain is a significant problem shown to affect up to 29% of patients with severe burn injury (Fredman 2016). The appearance of engrafted skin is often “abnormal”, resulting in social isolation and prejudice against patients with this condition. Overall, these problems present a significant health burden to survivors of major burns.

These patients would be required to have had a diagnosis of a burn as a prerequisite, and would need to be assessed by a specialist as having a burn scar (or skin graft for replacement of a burn scar) associated with significant contour deformity and causing significant mobility problems, dysaesthesias (being unpleasant abnormal sensations, such as burning or tingling), or deformity. To be eligible, the patient would be required to have undergone a minimum of three months of topical therapies, including silicone and pressure therapy, with an unsatisfactory (minimal) level of improvement. The proposed MBS item descriptor has been updated to include this.

The 2013–14 report on hospitalised burn injuries in Australia (AIHW 2016) indicates that, of the 5,430 persons hospitalised with burns in that financial year, 850 patients were considered high threat to life cases, 655 of whom had full thickness burns, indicating a significant incident burns population. The proportion of patients who may be refractory to alternative treatment options is not clear. As per the craniofacial patient population, most major burns patients are treated within the public hospital system (including in States and Territories that have major multidisciplinary private hospitals). The number of referrals into the private system (with associated MBS item billing) is therefore likely to be low.

However, the applicant advised that patients seeking secondary surgery (because of treatment failure and/or patient preference to receive treatment in a private hospital setting) will most likely be the target population who are refractory to other treatments. Secondary surgery is the surgery received after the acute burn surgery (and care) has been completed and the burn healed. Expert advice is that a burn has healed when it has re-epithelialised without ulceration.

The Burns Unit at the Austin Hospital in Melbourne reports an estimated 45 patients per year undergo surgery for hand or face burns that require grafts or having significant scarring problems, translating to approximately 180 patients nationally per year. If 10% of patients seek secondary treatment and are suitable for fat grafting, it is estimated that approximately 18-20 patients would be eligible for the service on an annual basis. This appears to only refer to adult burn patients. However, in Melbourne, the Royal Children’s Hospital has a burns unit, so children and adolescents will also need to be estimated.

Assuming an average of 3-5 services per patient, the total number of services used in this population is estimated to be 60-100 per annum (based on clinical expert correspondence provided by the applicant). It was noted that a pre-existing prevalent patient population who are refractory to alternative treatment options may exist, which could result in a higher utilisation of AFG in the first 1-2 years following MBS listing.

Based on evidence cited in Part 4 of the application form, non-burn scars may also benefit from AFG treatment. However, the applicant has not included these patients in the proposed population for AFG, given the large population size and lower clinical need.

Rationale

Burn scars are often refractory to standard treatments or require significant complex surgery to treat. This results in contractures and chronic pain, with an adverse impact on quality of life.

Attempts at scar modulation (with modalities including massage therapy, silicone gel sheeting, occupational therapy, steroid injections, and laser therapy) have been used with some success, but results in some patients have not been successful. Patients usually require daily medications and are often dependent on narcotic, antipruritic, anticonvulsant, and antidepressant medications, significantly limiting their quality of life. Nerve release, nerve transposition, intraneural neurolysis, nerve repair, and neuroma resection, even when combined with adjacent tissue rearrangement and flap reconstruction, have variable results and require prolonged rehabilitation and recovery.

In addition to management of dysaesthesias of hypertrophic scarring, surgical excision and split skin grafting often results in contour deformity and poor skin quality. Replacement of soft tissue defects associated with scarring and thin split skin grafts, results in restoration of contour and improved tissue quality and pliability.

The management of scars and burns using AFG utilises the regenerative capacity of adipose-derived stem cells (ADSCs), including in regeneration of skin and subcutaneous tissue with an increased fat layer, local neo-angiogenesis and new collagen deposition.

The description of the proposed population has been modified to ensure that it is sufficiently broad enough to capture the patient population with the greatest clinical need but specific enough to avoid inappropriate use of the intervention in unintended populations

AFG is therefore proposed to be used in patients with:

- **Burns scars anywhere on the body, not responding to topical and other conventional therapies and requiring treatment of dysaesthesias, contracture, poor skin quality or deformity**

Eligibility for AFG would require patients to have a suitable donor site for fat harvest.

Intervention

Autologous fat grafting (AFG) is the harvesting, preparation, and re-injection of autologous fat, with or without specialised fat grafting equipment. It includes live fat or adipose tissue being harvested from a donor site on the patient, typically the thigh, lower abdomen or flank, and transferred to another site via injection. Many of the studies that use AFG, particularly in the burn scar population, include AFG that also has a supplement added. For example, autologous stromal vascular fraction, autologous platelet rich plasma, basic fibroblast growth factor or insulin. It remains to be determined if these supplements are approved by the TGA and if they are, whether the intervention is defined as AFG alone or AFG + supplement.

Coleman (1997) established a method for autologous fat transfer (AFT) involving harvesting fat with atraumatic liposuction, purifying adipocytes with centrifugation and then injection in another body site (breast, face, burn or scar). Other methods have been developed, that refine some of these core elements such as additional washing of the aspirate, or which propose the use of additives including insulin, platelet rich plasma, endogenous stem cells, and thyroid hormone, or harvesting of the fat at multiple sessions (Illouz et al., 2009). The applicant stated that AFG in Australia would not usually include the addition of additives. PASC noted that the use of AFG could be with/without additives. PASC considered the assessment report should stratify the results by use of AFG so any treatment effect modification with addition of additives to AFG can be assessed.

The approach relies on the fat stem cells remaining viable in the transferred site. The viability of adipocytes has been shown to decrease with increased suction, excessive handling, refrigeration or major trauma during tissue collection or processing (Chan et al., 2008). Whilst the preparation can be performed manually there is now commercially available technology that uses systems to streamline the graft preparation process by selectively washing lipoaspirate while draining any unwanted tumescent fluid, free lipid, and debris has been developed. These systems can prepare 50 to 250 ml of graft in a closed, sterile environment in less than 15 minutes and allow the user to define the hydration level of the final graft (Wetterau et al., 2016).

In a systematic review of AFG for burn scars (Riyat et al, 2017), the volume injected was in the range of 0.5 to 80 mls across 15 studies. ". Riyat et al 2017 also indicated that the volume injected was proportional to the extent of scarring and surface area affected.

The applicant did not indicate graft volumes needed for craniofacial abnormalities. However, there were no craniofacial cases in the systemic review, as they did not meet the inclusion criteria. The focus of the review by Riyat et al was on pain and relief of scar symptoms, not correction of contour deformity.

Harvest and transplant procedures can usually be completed within two hours (as opposed to up to ten hours for free autologous flap reconstruction). PASC noted the increased speed of the intervention (around 2 hours), compared with at least 10 hours for microsurgery of vascularised tissue. *Please note that this PICO document mainly uses the term 'free autologous flap reconstruction' (not microsurgery of vascularised tissue). For all intents and purposes, these are the same thing, so the term 'free autologous flap' has been maintained.*

Donor sites used are usually from the lower abdomen or the outer or inner thigh, with the thigh more resistant to weight fluctuation. There is no difference in the ability of these sites to produce proliferating cells in culture.

In positioning the graft most surgeons use a blunted-tip cannula to deliver the processed fat in multiple passes. The technique is designed to deliver thin layers of fat that will survive by imbibition until inosculation and neovascularization occur. Recipient site studies have demonstrated that mobile areas, such as the lips, are less amenable to correction when compared to less mobile areas.

AFG is to be used in an operating theatre as a day-case surgical procedure or part of a more extensive procedure requiring a longer admission. Craniofacial defects and burns may require up to 6 procedures, but most will require 1-2 treatments. As fat resorption occurs preferentially in the first 3 months, there should be a limit that fat grafting cannot be repeated within 3 months of each treatment. Reassessment by the treating specialist and monitoring with clinical photography between each treatment should also be mandatory.

Rationale

The application of AFG differs depending on the population and purpose of treatment:

Population 1: AFG may be used alone, or with other surgical procedures other than to the craniofacial region to improve facial tissue deficiencies, volume differences and contour.

Population 2: AFG may be used alone, or with other procedures, and usual care.

AFG can be used in women 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) as well as women with developmental breast abnormalities. The use of AFG in these indications is addressed within a separate application (1575).

Comparator

PASC considered that for population 1:

- For those with congenital or acquired facial asymmetry and willing to undergo invasive surgical procedures: bony reconstruction and/or free autologous flap reconstruction is an appropriate comparator. PASC noted this procedure often requires subsequent revision surgery.
- For those with congenital or acquired facial asymmetry and unwilling to undergo invasive surgical procedures: usual care is the appropriate comparator.

PASC acknowledged the lack of appropriate comparators for population 2; usual care is often the only option.

Population 1: Craniofacial disorders with facial asymmetry

Comparative treatments for facial tissue deficiencies would typically require treatment with bony reconstruction and/or a free autologous flap (MBS items 45564 and 45565; Table 3). This would usually be performed with an anaesthetic of longer than 6 hours and an inpatient hospital stay of 7 days. For this group of patients, ICU stay would be common for the first 24 – 48 hours of post-operative care. Equipment and disposables costs would be significant. Revision of the free flap years down the track is very common and would need further anaesthetics and 45496 item number.

In some cases, patients with craniofacial disorders may simply not wish to undergo such invasive surgery. In the absence of AFG, these patients would continue with usual care comprising, but not limited to, psychological attendances, ophthalmology appointments, speech therapies, and other allied health services.

Table 3 MBS item descriptors of the comparator treatments, POPULATION 1: Craniofacial abnormalities

Category 3 - THERAPEUTIC PROCEDURES		
45564	Group	T8 - Surgical Operations
	Subgroup	13 - Plastic And Reconstructive Surgery
	Subheading	4 - Other Grafts And Miscellaneous Procedures
Free transfer of tissue reconstructive surgery for the repair of major tissue defect due to congenital deformity, surgery or trauma, involving anastomoses of up to 2 vessels using microvascular techniques and including raising of tissue on a vascular or neurovascular pedicle, preparation of recipient vessels, transfer of tissue, inseting of tissue at recipient site and direct repair of secondary cutaneous defect if performed, other than a service associated with a service to which item 30165, 30168, 30171, 30172, 30176, 30177, 30179, 45501, 45502, 45504, 45505 or 45562 applies-conjoint surgery, principal specialist surgeon (H)		
Multiple Operation Rule (Anaes.) (Assist.)		

Category 3 - THERAPEUTIC PROCEDURES

Fee: \$2,587.05 Benefit: 75% = \$1,940.30

(See para TN.8.8 of explanatory notes to this Category)

45565 Group T8 - Surgical Operations
 Subgroup 13 - Plastic And Reconstructive Surgery
 Subheading 4 - Other Grafts And Miscellaneous Procedures

Free transfer of tissue reconstructive surgery for the repair of major tissue defect due to congenital deformity, surgery or trauma, involving anastomoses of up to 2 vessels using microvascular techniques and including raising of tissue on a vascular or neurovascular pedicle, preparation of recipient vessels, transfer of tissue, inseting of tissue at recipient site and direct repair of secondary cutaneous defect if performed, other than a service associated with a service to which item 30165, 30168, 30171, 30172, 30176, 30177, 30179, 45501, 45502, 45504, 45505 or 45562 applies-conjoint surgery, conjoint specialist surgeon (H)

Multiple Operation Rule

(Assist.)

Fee: \$1,940.35 Benefit: 75% = \$1,455.30

(See para TN.8.8 of explanatory notes to this Category)

TN.8.8

Lipectomy - (Items 30165 to 30179)

Lipectomy is not intended as a primary bariatric procedure to correct obesity. MBS benefits are not available for surgery performed for cosmetic purposes.

For the purpose of informing patient eligibility for lipectomy items (30165-30172, 30177, 30179) that are for the management of significant weight loss (SWL), SWL is defined as a weight loss equivalent of at least five BMI units. Weight must be stable for at least six months following significant weight loss prior to lipectomy. For significant weight loss that has occurred following pregnancy, the products of conception must not be included in the calculation of baseline weight to measure weight loss against.

Multiple lipectomies of redundant non-abdominal skin and fat as a direct consequence of mass weight loss (for example on both buttocks and both thighs), attracts a Medicare benefit only once against the relevant item (30171 or 30172). The schedule fee for multiple lipectomies for excision of redundant non-abdominal skin and fat following massive weight loss is the same regardless of the number of excisions.

The lipectomy items cannot be claimed in association with items 45564, 45565 or 45530. Where the abdomen requires surgical closure with reconstruction of the umbilicus following free tissue transfer (45564, 45565) or breast reconstruction (45530), item 45569 is to be claimed.

Population 2: Burn scars and contractures

AFG is to be used in patients with burn scars who have previously undergone surgery and who have been shown to be refractory to conservative treatment methods (such as physiotherapy, pain relief topical treatments and compression garments). Further surgery or continued use of conservative measures in these patients is considered to provide limited additional benefit to the patients. Consequently, usual care (UC) is considered to be the most appropriate comparator.

In the absence of other available treatments (and given the high clinical need in these patients), the applicant advised that further surgery may still be attempted, despite diminished benefit. Such procedures may include scar contracture release (MBS item 45519; Table 4), repeat skin grafting (MBS item 45451; Table 5) or sometimes pedicle flap (MBS item 45203; Table 6). Depending on how frequently these secondary procedures are performed in this population, revision surgery may also be considered an additional comparator).

Table 4 MBS items of the comparator treatments (scar contracture release), POPULATION 2: burn scars and contractures

Category 3 - THERAPEUTIC PROCEDURES		
45519	Group Subgroup Subheading	T8 – Surgical Operations 13 – Plastic and Reconstructive Surgery 4 – Other Grafts and Miscellaneous Procedures
EXTENSIVE BURN SCARS OF SKIN (more than 1 percent of body surface area), excision of, for correction of scar contracture		
Multiple Operation Rule (Anaes.) (Assist.)		
Fee: \$435.90 Benefit: 75% = \$326.95		

Table 5 MBS items of the comparator treatments (skin grafting), POPULATION 2: burn scars and contractures

Category 3 - THERAPEUTIC PROCEDURES		
45451	Group Subgroup Subheading	T8 – Surgical Operations 13 – Plastic and Reconstructive Surgery 3 – Free Grafts
FREE GRAFTING (full thickness), to 1 defect, excluding grafts for male pattern baldness		
Multiple Operation Rule (Anaes.) (Assist.)		
Fee: \$481.35 Benefit: 75% = \$361.05 85% = \$409.15		

Table 6 MBS items of the comparator treatments (pedicle flap), POPULATION 2: burn scars and contractures

Category 3 - THERAPEUTIC PROCEDURES		
45203	Group Subgroup Subheading	T8 – Surgical Operations 13 – Plastic and Reconstructive Surgery 2 – Skin Flap Surgery
Single stage local flap, if indicated to repair one defect, complicated or large, excluding flap for male pattern baldness and excluding H-flap or double advancement flap not in association with any of items 31356 to 31376		
Multiple Operation Rule (Anaes.) (Assist.)		

Category 3 - THERAPEUTIC PROCEDURES

Fee: \$412.55 Benefit: 75% = \$309.45 85% = \$409.15

(See para TN.8.93 of explanatory notes to this Category)

Extended Medicare Safety Net Cap: \$330.05

Outcomes

PASC recommended that skin breakdown and risk of infection be added to the outcomes. PASC acknowledged that evidence for risk of infection post-procedure may be limited.

PASC accepted the appropriateness of mental health, psychosocial effect and similar outcomes for this intervention. PASC noted there are currently no suitable measures for these outcomes.

PASC noted AFG would not be used for tissue expansion in preparation for further surgery.

A range of patient and health system related outcomes expected to be affected by introduction of the proposed service were identified from the extant literature.

Patient-relevant outcomes

The relevant outcomes are specific to the clinical management plan for each population.

Population 1: Craniofacial disorders with facial asymmetry

For patients with craniofacial disorders, patient-relevant outcomes relate to patient acceptance of outcome, and clinical judgement of the surgeon; quality of life; volume retention; irregularities of surface or contour; and aesthetic outcome. These are listed below.

- Patient acceptance of outcome, and clinical judgement of the surgeon
- Volume retention: % of volume gain relative to injected volume
- Health-related quality of life

Population 2: Burn scars and contractures

For patients with burn scars and contractures, AFG may be used to alleviate symptoms such as pain and discomfort, and/or to improve function where contractures have resulted in reduced functional capabilities, or to improve aesthetics. Specifically:

- Patient acceptance of outcome
- Pain and itch relief (POSAS/VAS)
- Restored function/mobility
- Scar characteristics (assessed using POSAS) including:
 - Hardness/Thickness
 - Colour
 - Texture
 - Contour
 - Pliability
 - Mobility
- Volume retention: % of volume gain relative to injected volume
- Health-related quality of life

Safety outcomes

For both populations 1 and 2, relevant safety outcomes include donor and reinjection site complications such as calcifications, necrosis and infection.

- Complications:
 - Donor site:
 - Local infection;
 - Deep vein thrombosis
 - Abdominal organ injury
 - Haematoma/bleeding
 - Change to skin sensation
 - Scarring
 - Skin breakdown
 - Reinjection site:
 - Fat necrosis
 - Cysts
 - Infection
 - Post-operative pain
 - Scarring
 - Contour irregularities

Economic outcomes:

All populations:

- Number and cost of fat grafting sessions
- Quality adjusted life years (QALYs)

Economic outcomes relevant to **Population 1** include:

- Cost of comparator (autologous flap) operations

Economic outcomes relevant to **Population 2** include:

- Cost of secondary surgeries (when applicable) and other resources used for usual care

Changes in outcome measures and quality of life over time should be considered, and long-term outcomes will need to be modelled with appropriate assumptions.

The cost of donor and reinjection site complications should also be included.

The applicant queried whether costs of non-treatment were relevant to economic outcomes (i.e. in the absence of treatment, burn contractures can result in mobility defects and loss of productivity, and unstable scarring can result in spontaneous ulcers, with associated infection-related hospital admissions). PASC advised that, as per the *Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee – Medical Service Type: Therapeutic (Version 2.0)*, a claim for a change in non-health care resource costs or in non-health outcomes (e.g. production changes) could be presented as a supplementary analysis for the economic evaluation.

Healthcare system

AFG can be performed in an operating theatre as day surgery, or part of a more extensive procedure, requiring longer hospital admission. It usually takes 30 to 60 minutes of operating theatre time. Depending on the population and outcomes of the procedure, up to five sessions may

be required, with a median of two sessions. There is usually a three-month (12 week) interval between procedures. The AFG procedure requires a nursing team, a surgeon and an anaesthetist. The resources required are typical of any surgery and, as such, there should be no specific access issues for AFG if it was to be included on the MBS.

The likely consequences of AFG for the healthcare system, including changes in patterns of healthcare resource provision, are described below with respect to each of the main patient populations (identified in Table 1 and Table 2 above).

Population 1: Craniofacial abnormalities

Patients with craniofacial abnormalities currently require surgical intervention, comprising bony reconstruction and/or autologous flap reconstruction (MBS items 45564 and 45565). This would usually be performed with an anaesthetic of longer than 6 hours and an inpatient hospital stay of 7 days. For this group of patients, ICU stay would be common for the first 24 – 48 hours of post-operative care. Equipment and disposables costs would be significant. Revision of the free flap years down the track is very common and would need further anaesthetics and 45496 item number.

As a less invasive procedure, it is anticipated that AFG will likely result in a reduction in utilisation of health care services. However, PASC noted that this patient population includes heterogeneous conditions, which would impact the utilisation of health care services.

For patients who would choose not to undergo invasive surgery but who may be suitable for reconstruction with AFG alone, AFG may increase utilisation of health care resources.

Population 2: Burn scars and contractures

The comparator for population is usual care. Consequently, AFG will likely add to the utilisation of health care services comprising the AFG procedure itself and any additional resources required following complications from the service.

Where secondary surgery could be considered an additional comparator, AFG will likely reduce utilisation of health care services through a reduction in other more invasive surgical procedures that may be more costly and require a longer hospital length of stay.

Resources required to manage the pain and discomfort of the burn scar and contracture could be expected to be reduced following a successful AFG procedure.

Rationale

Outcomes of interest are based on the outcomes presented in the pivotal systematic reviews listed in the application form and identified from the literature (Krastev 2018, Riyat 2017, Negenborn 2016, Condé-Green 2016). Outcomes of interest include both structural and patient reported outcomes. Mean follow-up time for outcome assessment ranged from 6 to 66 months in the pivotal systematic reviews.

The provided systematic reviews used a range of scales and instruments to measure outcomes, including the Patient and Observer Scar assessment Scale (POSAS) for the assessment of scar characteristics and pain, VAS pain scores, Likert scales to determine satisfaction of the patient, and/or clinical judgement of the surgeon,; CT imaging to determine volume measurements.

While the applicant suggests that improvement in health-related quality of life is an important outcome, it is unclear how this is assessed in the literature.

Important safety endpoints suggested by the applicant and identified in the provided systematic reviews include the donor and reinjection site complications listed above. These safety outcomes are considered important endpoints and are included as recommended outcomes. The Clavien-Dindo scale was identified in the provided systematic review, Agha et al. (2015), as a scale to grade severity of AFG complications in breast reconstructions however, this does not appear to have been applied in the safety assessment of AFG in patients with burns scars or craniofacial abnormalities.

Additional outcomes that are not related to clinical efficacy or safety include duration of surgery, length of hospital stay, and time to recovery from the procedure and surgeries. While not specifically patient relevant, these outcomes are relevant to the assessment of cost effectiveness.

Current clinical management algorithm for identified population

There are no guidelines depicting clinical management algorithms for AFG in either population.

The algorithms below were constructed in consultation with the applicant, and updated after PASC’s consideration.

Population 1: Craniofacial disorders with facial asymmetry

The current clinical management algorithm for patients in population 1 (i.e. patients diagnosed with craniofacial disorders with facial asymmetry) is provided in

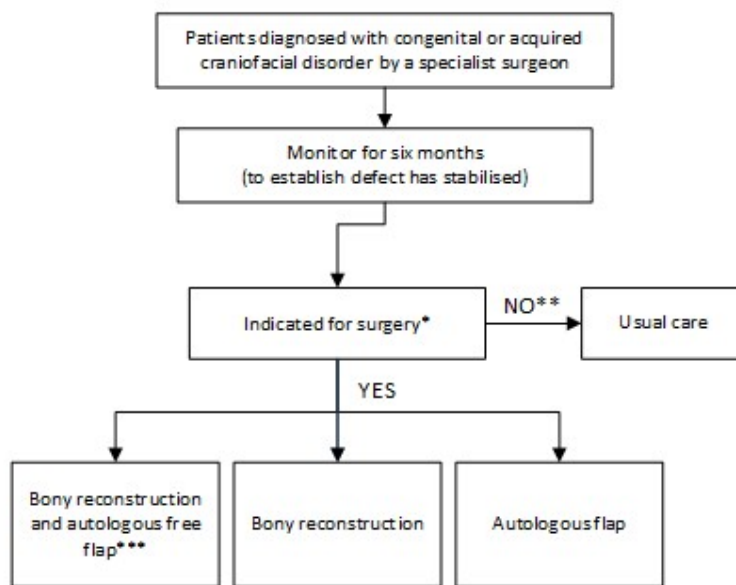


Figure 1. The algorithm depicts current practice in the absence of public funding for the proposed medical service. For this population, usual care (UC) refers to ongoing symptomatic management without surgical intervention including psychological attendances.

Patients are required to have had a formal diagnosis of a craniofacial disorder and be assessed by a specialist as having a significant facial asymmetry or contour defect identified by clinical evaluation by a specialist and documented by clinical photography. Laser scanning or MRI scanning may be ordered. Referral is provided by a GP or other specialist (e.g. paediatrician) to a specialist in the field (plastic and reconstructive surgeon, or oromaxillofacial surgeon).

Patients are monitored in a multidisciplinary specialist team, including paediatricians, speech pathologists, plastic surgeons and nutritionists. For some, significant craniofacial surgery would be

indicated as first line treatment for correction of craniofacial abnormalities, for others, autologous fat grafting may be a first line treatment of choice as it presents significantly less morbidity and risk than major surgery. At a minimum, prior to surgery, patients are required to have had monitoring of their condition over a period of at least 6 months in order to establish that the defect had stabilised, with clinical assessment and clinical photography.

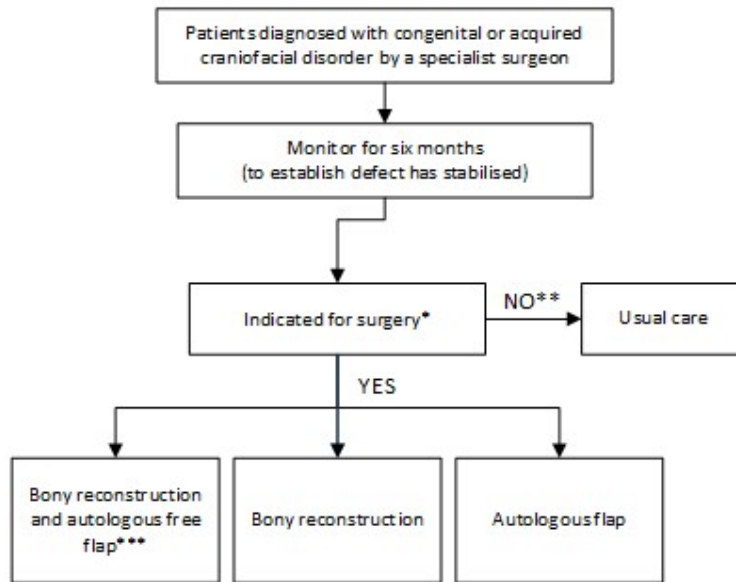


Figure 1 Clinical management pathway of current clinical practice - Population 1

Abbreviations: UC, Usual care

Note: Indication for surgery includes patient preference (i.e. patients who do not wish to undergo invasive surgery continue with usual care)

*Could be first- or subsequent-line (likely subsequent-line in private setting)

**Not suitable for surgery or not willing to undergo invasive surgery

***In single surgery or autologous flap/AFG subsequent to bony reconstruction

Population 2: Burn scars and contractures

Figure 2 presents the current clinical algorithm for patients with burn scars (population 2).

Referral would be by a GP (or other specialist) to a specialist with expertise in burns (Plastic and Reconstructive Surgeon, General Surgeon or Paediatric Surgeon).

Patients would be assessed by a specialist surgeon in burns, following the complete healing of burn wounds/associated skin grafts, in order to determine suitability for surgery. In the case of acute and immature scars, patients may be monitored for a period of up to 6 months to determine the most appropriate time for surgery during which time, conservative therapies may be used. Surgery may be performed to release contractures or perform a skin graft to the burn site. Should symptoms persist, alternative topical therapies including silicone and pressure therapy can be used.

The figure depicts the limited treatment options available to the patient should there be no discernible improvements following initial surgery and at least 3 months of alternative therapies including pressure therapy and topical silicone. That is, to choose further surgery or to do nothing.

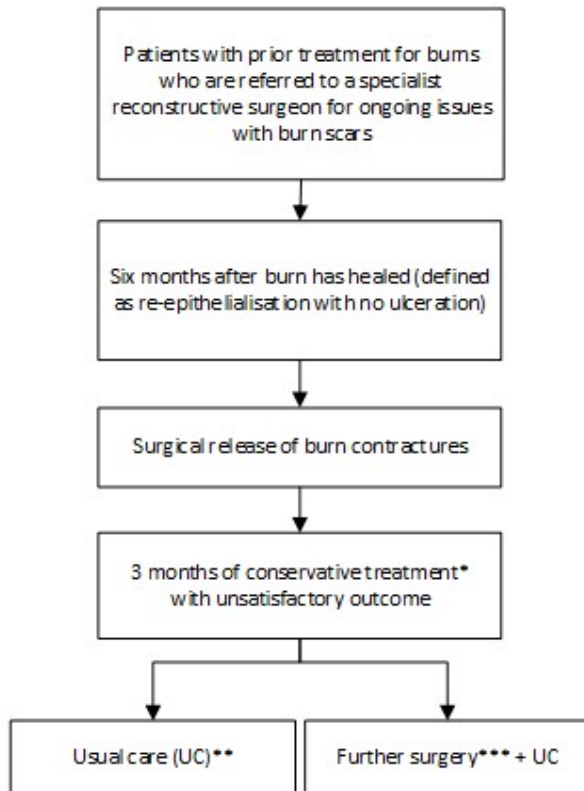


Figure 2 Clinical management pathway of current clinical practice - Population 2

Abbreviations: UC, usual care

*Conservative treatment refers to silicone, pressure garments and physiotherapy (laser treatment may also be included)

**Usual care (UC) = conservative treatment e.g. physiotherapy, pain relief, lotions, laser therapy

***For example, scar contracture release (MBS item 45519), repeat skin grafting (MBS item 45451), or pedicle flap (MBS item 45203)

Proposed clinical management algorithm for identified population

Population 1: Craniofacial disorders with facial asymmetry

PASC confirmed that AFG should not be as a first-line treatment after diagnosis, but rather performed after a typical six month monitoring period ensuring that the defect has stabilised and patient could be indicated for surgery.

The proposed clinical management for population 1 is presented in Figure . Should AFG be available, specialist reconstructive plastic surgeons may assess whether a patient may benefit from AFG alone without invasive bony and/or autologous flap reconstruction. Should invasive surgery be required, AFG may also be used following invasive surgery to correct persisting asymmetries or deformity.

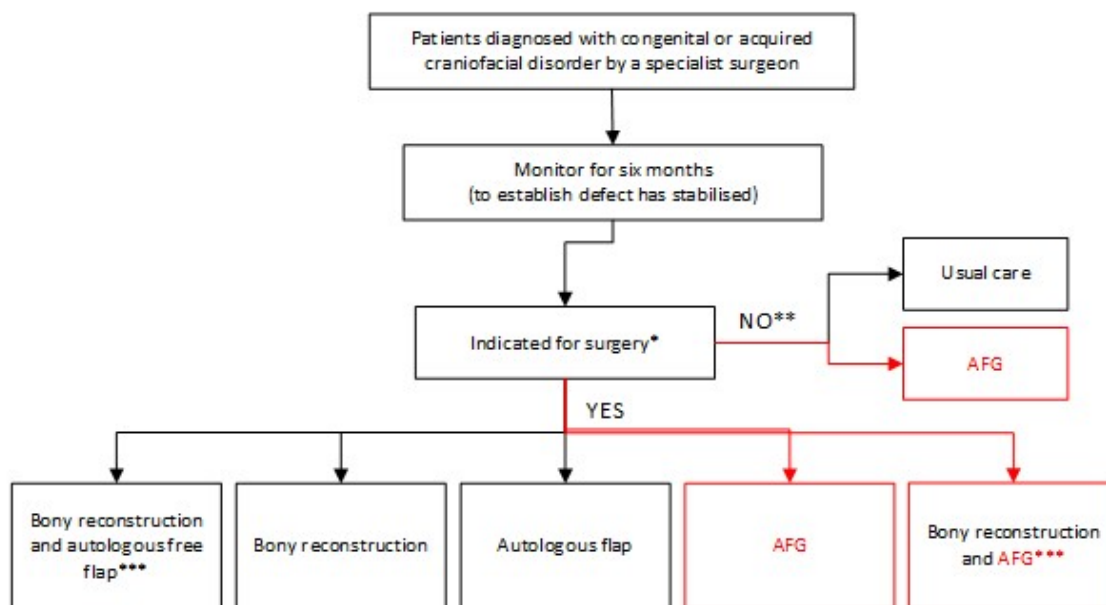


Figure 3 Proposed clinical algorithm for population 1

Abbreviations: UC, usual care; AFG = autologous fat grafting

*Could be first- or subsequent-line (likely subsequent-line in private setting)

**Not suitable for surgery or not willing to undergo invasive surgery

***In single surgery or autologous flap/AFG subsequent to bony reconstruction

Population 2: Burn scars and contractures

The proposed clinical management for population 2 is presented in Figure . In the clinical algorithm, AFG is positioned as a last line therapy, with the patient needing to have undergone a minimum of 3 months of topical therapies, including silicone and pressure therapy, with an unsatisfactory (minimal) level of improvement.

The service is to be used in place of, or in conjunction with, UC.

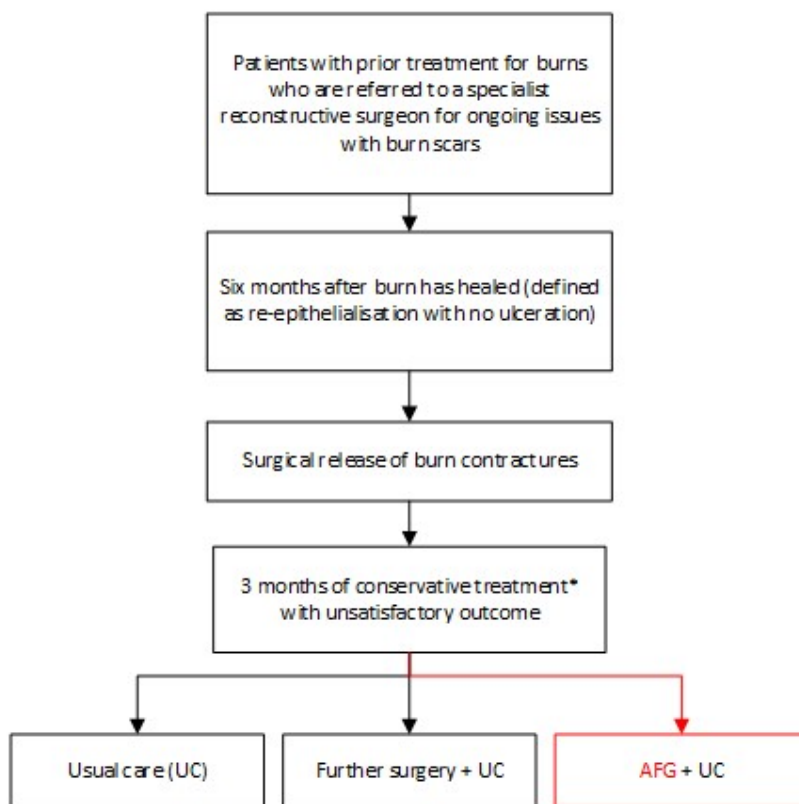


Figure 4 Proposed clinical algorithm for population 2

Abbreviations: UC, usual care; AFG, Autologous fat grafting

*Conservative treatment refers to silicone, pressure garments and physiotherapy (laser treatment may also be included)

**Usual care (UC) = conservative treatment e.g. physiotherapy, pain relief, lotions, laser therapy

***For example, scar contracture release (MBS item 45519), repeat skin grafting (MBS item 45451), or pedicle flap (MBS item 45203)

Proposed economic evaluation

PASC confirmed the economic evaluation for the burns population could be a cost-utility or cost-effectiveness analysis to match the clinical claims of the intervention for the burns population (i.e. superiority). The clinical claim for the craniofacial disorders population is non-inferiority, thus a cost-minimisation analysis is appropriate.

Population 1: Craniofacial abnormalities

The proposed service is expected to achieve non inferior efficacy as surgical comparator services, but with superior safety and fewer associated resource requirements.

Where AFG is used in place of bony and/or autologous flap reconstruction, the form of economic evaluation will largely depend upon the comparative safety and efficacy of AFG. On the basis that a clinical claim of non-inferiority can be substantiated, a cost-minimisation analysis would be appropriate. This analysis would need to include costs of any downstream resources. For instance, it is anticipated AFG could be less costly overall than a repeat surgical procedure. However, it might also be the case that AFG does not successfully resolve the defect(s), with surgery still being required. It would be reasonable for the cost-minimisation analysis to include these possibilities. However, PASC noted this patient population is heterogeneous, and the cost of any downstream resources would depend on the underlying condition.

Population 2: Burn scars and contractures

The proposed service for this group of patients offers further remediation of the pain, deformity and functional deficit associated with major burns scarring where primary surgery to release of contracture and skin graft followed by conservative treatments (defined as UC) have failed to improve or alleviate symptoms. Another comparator for some patients is a secondary surgery to release contracture, skin graft or pedicle flap.

Since AFG is used in place of, or adjunct to, usual care in patients who are refractory to conservative treatment, a clinical claim of superior efficacy and effectiveness is expected and cost-utility or cost-effectiveness analysis is the appropriate form of economic evaluation.

Proposed item descriptor and MBS fee

PASC noted that, for the burn item, the burn can be anywhere on the body.

PASC acknowledged the request for photographic evidence and consistent phrasing with other similar item descriptors, including that proposed for earlier Application 1575 – *Autologous fat grafting (AFG) by injection, for defects arising from breast surgery, breast cancer treatment/prevention and congenital breast deformity.*

PASC agreed that appropriate phrasing would be: “photographic and/or imaging evidence, demonstrating the clinical need for this service, which is to be documented in patient notes”.

PASC queried the number of services; the applicant stated that 1–2 is often enough, up to a maximum of 5. PASC noted that fat reabsorption is an issue, and that most reabsorption takes place in the first 3 months post-treatment. The grafted fat then remains stable for at least 12 months. PASC accepted that a maximum of 5 services over a lifetime, with at least 3 months in between services, is appropriate.

PASC agreed that the procedure be available to children and adults, but noted that not all 5 sessions would be needed in childhood – some would occur once the patient reached adulthood.

The MBS fee for AFG (proposed by the applicant) is based on the MBS fee for liposuction (MBS items 45584 and 45585), applies to each service, and reflects professional costs of the surgeon and equipment costs. According to the applicant, this is considered a reasonable fee, because AFG requires slightly more time and use of additional equipment for re-injection of fat.

Another aspect of the liposuction item descriptor which may be of relevance to AFG is the requirement for photographic and/or imaging evidence demonstrating the clinical need for this service to be documented in the patient notes. Such a requirement may serve as a method to ensure AFG is only used for patients where it is warranted and to minimise leakage.

For the treatment of craniofacial abnormalities, the proposed service is to be used for a maximum of five sessions. The same number of services is permitted for the treatment of burn scars. However, on the basis that patients with severe burns may have more than one burn scar requiring treatment, it is not possible to determine from the current proposed item descriptor whether the maximum number of services is permitted per scar, per patient (i.e. per “episode”) or whether it is per patient over their life time.

Proposed item descriptor

Category T8 – Plastic and Reconstructive Surgery

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 asymmetry arising from volume and contour defects in craniofacial disorders, up to a maximum of 5 services per episode, with at least 3 months between services; OR
 - (ii) treatment of burn scar or associated skin graft in the context of scar contracture, contour deformity or neuropathic pain, in patients who have undergone a minimum of 3 months of topical therapies, including silicone and pressure therapy, with an unsatisfactory (minimal) level of improvement; up to a maximum of 5 services per region of the body defined as upper or lower limbs, trunk, neck or face; with at least 3 months between services in the same region; AND
- (b) photographic and/or imaging evidence, demonstrating the clinical need for this service, is to be documented in patient notes; AND
- (c) in relation to craniofacial disorders, evidence of diagnosis of the qualifying craniofacial disorder is documented in patient notes

Multiple Operation Rule

(Anaes.)

MBS Fee: \$641.85 Benefit: 75% = \$481.40

Consultation feedback

PASC noted the letter of support from the applicant for the craniofacial disorders population. PASC recommended that feedback be sought from burns groups.

Next steps

Upon ratification of PICO 1577, it can PROCEED to the pre-Evaluation Sub-Committee (ESC) stage, with the applicant opting for a DCAR (Department-contracted assessment report).

For consistency, earlier application 1575 (for the same product; different population) should be cross-referenced with 1577. It may be efficient if the same HTA group undertakes the assessment report for 1577 as that which evaluated earlier application 1575.

References

- Agha R, Fowler A, Herlin C, et al. Use of autologous fat grafting for breast reconstruction: A systematic review with meta-analysis of oncological outcomes. *International Journal of Surgical Reconstruction*. 2015;68:143-161.
- Coleman SR. Facial recontouring with lipostructure. *Clin Plast Surg*. 1997; 24, 347-67.
- Condé-Green, A., et al. (2016). "Fat grafting and adipose-derived regenerative cells in burn wound healing and scarring: a systematic review of the literature." *Plastic and Reconstructive Surgery* **137**(1): 302-312
- Fredman R, Edkins RE, Hultman CS. Fat Grafting for Neuropathic Pain After Severe Burns. *Ann Plast Surg*. 2016 Jun;76 Suppl 4:S298-303.
- Illouz YG, 2009. Autologous fat transplantation to the breast: a personal technique with 25 years of experience. *Aesthetic Plastic Surgery*, 2009; 33, 706-715.
- Krastev TK, Beugels J, Hommes J, Piatkowski A, Mathijssen I, van der Hulst R. Efficacy and Safety of Autologous Fat Transfer in Facial Reconstructive Surgery: A Systematic Review and Meta-analysis. *JAMA Facial Plast Surg*. 2018;20(5):351–360. doi:10.1001/jamafacial.2018.0102
- Negenborn, V. L., et al. (2016). "The Use of Autologous Fat Grafting for Treatment of Scar Tissue and Scar-Related Conditions: A Systematic Review." *Plast Reconstr Surg* **137**(1): 31e-43e
- Riyat H, Touil LL, Briggs M, Shokrollahi K. Autologous fat grafting for scars, healing and pain: a review. *Scars Burn Heal*. 2017;3:2059513117728200. Published 2017 Sep 18.
- Singh VP, Moss TP. Psychological impact of visible differences in patients with congenital craniofacial anomalies. *Prog Orthod*. ;16:5. doi:10.1186/s40510-015-0078-9
- van den Elzen ME, Versnel SL, Hovius SE, Passchier J, Duivenvoorden HJ, Mathijssen IM. Adults with congenital or acquired facial disfigurement: impact of appearance on social functioning. *J Craniomaxillofac Surg*. 2012 Dec;40(8):777-82.
- Versnel SL, Duivenvoorden HJ, Passchier J, Mathijssen IM. Satisfaction with facial appearance and its determinants in adults with severe congenital facial disfigurement: a case-referent study. *J Plast Reconstr Aesthet Surg*. 2010 Oct;63(10):1642-9.
- Visram SM, Gill D, Shute JT, Cunningham SJ. Qualitative study to identify issues affecting quality of life in adults with craniofacial anomalies. *Br J Oral Maxillofac Surg*. 2019 Jan;57(1):47-52.
- Wetterau M, Szpalski C, Hazen A, Warren S. Autologous Fat Grafting and Facial Reconstruction. *Plast Reconstr Surg*. 2016; Jan 137(1):31e-43e.
- Yıldız T, Selimen D. The Impact of Facial Aesthetic and Reconstructive Surgeries on Patients' Quality of Life. *Indian J Surg*. 2015;77(Suppl 3):831–836. doi:10.1007/s12262-013-1024-z