

## **MSAC Application 1773**

**Autologous chondrocyte implantation for  
symptomatic articular cartilage defects  
greater than 2 cm<sup>2</sup> of the knee**

**Applicant: Wurley Group Pty Ltd**

# **PICO Confirmation**

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

Table 1 PICO for matrix-assisted autologous chondrocyte implantation (ACI) in patients with symptomatic chondral defects of the knee

Component	Description
Population	<p>Patients aged between 18 and 55 years who have failed conservative treatment of symptomatic, International Cartilage Repair Society (ICRS) grade 3 or 4, focal chondral or osteochondral defects of the knee in an otherwise normal joint (e.g. in the absence of rheumatoid or other inflammatory arthritic conditions, osteoarthritis or unstable or mal-aligned joints, unless being concurrently corrected), where lesions are at least 2 cm<sup>2</sup> but less than 20 cm<sup>2</sup> in size.</p> <p>Two lesion-sized sub-groups are to be considered:</p> <ul style="list-style-type: none"> <li>• 2 cm<sup>2</sup> to 4 cm<sup>2</sup></li> <li>• &gt; 4 cm<sup>2</sup> to &lt; 20 cm<sup>2</sup>.</li> </ul>
Intervention	Autologous chondrocyte implantation (ACI) using a collagen matrix scaffold.
Comparator/s	<p>Comparator for lesions 2 cm<sup>2</sup> to 4 cm<sup>2</sup>:</p> <ul style="list-style-type: none"> <li>• microfracture</li> </ul> <p>Comparator for lesions &gt; 4 cm<sup>2</sup> to &lt; 20 cm<sup>2</sup>:</p> <ul style="list-style-type: none"> <li>• watchful waiting (with conservative treatment)</li> </ul>
Outcomes	<p><b>Safety outcomes</b></p> <ul style="list-style-type: none"> <li>• serious adverse events such as arthralgia, cartilage injury, meniscus injury and development of osteoarthritis</li> <li>• device-related adverse events</li> <li>• surgery-related adverse events</li> </ul> <p><b>Efficacy/effectiveness outcomes</b></p> <ul style="list-style-type: none"> <li>• knee-specific functional measures such as: Knee Injury and Osteoarthritis Outcome Score (KOOS); Lysholm Knee Score; Tegner Activity Level Scale; Cincinnati Knee Rating Score (CKRS); International Knee Documentation Committee (IKDC) Subjective Knee Score</li> <li>• other functional outcomes such as the 'Six-minute walk test'</li> <li>• quality-of-life measures such as EuroQuol Group 5-Dimension Self Report Questionnaire (EQ-5D) and Short Form-36 (SF-36)</li> <li>• pain measures (e.g. visual analogue scale; VAS)</li> <li>• subsequent conservative treatment interventions to treat index lesion e.g. corticosteroid injections</li> <li>• subsequent surgical procedures to treat index lesion</li> <li>• rates of progression to joint replacement (i.e. total or partial knee arthroplasty)</li> <li>• compound treatment failure outcomes using any of the above</li> </ul> <p><b>Health care resources</b></p> <ul style="list-style-type: none"> <li>• cost of ACI and associated materials (i.e. collagen matrix scaffold and fibrin glue)</li> <li>• cost of procedure (i.e. proposed service fee; anaesthetist services; theatre/admission costs, including consumables)</li> </ul> <p><b>Cost-effectiveness</b></p> <p><b>Total Australian Government health care costs</b></p>

Assessment question	<p>What is the safety, effectiveness, cost-effectiveness and total costs of ACI using a collagen matrix scaffold versus microfracture in patients who have failed conservative treatment of symptomatic, ICRS grade 3 or 4 focal chondral or osteochondral defects of the knee from 2 cm<sup>2</sup> to 4 cm<sup>2</sup> in size?</p> <p>What is the safety, effectiveness, cost-effectiveness and total costs of ACI using a collagen matrix scaffold versus watchful waiting (with conservative treatment) in patients who have failed conservative treatment of symptomatic, ICRS grade 3 or 4 focal chondral or osteochondral defects of the knee from &gt; 4 cm<sup>2</sup> to &lt; 20 cm<sup>2</sup> in size?</p>
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ACI = autologous chondrocyte implantation; ICRS = International Cartilage Repair Society.

## Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of two new MBS items for autologous chondrocyte implantation (ACI) using a collagen matrix scaffold for the treatment of symptomatic chondral lesions of the knee at least 2 cm<sup>2</sup> but less than 20 cm<sup>2</sup> in size was received from Wurley Group Pty Ltd by the Department of Health and Aged Care. The applicant product is a cellular therapy OrthoACI – which is a registered trademark in Australia. This is the first application for ACI by this applicant and is for ACI implanted using a collagen matrix scaffold. This implantation technique has typically been referred to by the generic term ‘MACI’, indicating matrix-assisted/induced/applied/guided ACI; however, the term was trademarked in Europe (2013) and the USA (2016) by Vericel Corporation (Kim et al. 2022). The current application refers to the proposed intervention variously as MACI or ACI, but henceforth, the intervention proposed by the current application will be referred to as matrix-assisted ACI.

Prior PASC and MSAC considerations of various interventions for chondral and osteochondral lesions of the knee are listed in Table 2. In December 2010, MSAC considered an application [1140](#) for ACI/MACI for the treatment of articular cartilage defects (submitted by Genzyme, Biotech Regulatory Solutions and Device Technologies Australia). MSAC did not support public funding for the technology at that time due to ‘increased costs compared to existing procedures and the lack of evidence showing short-term or long-term improvements in clinical outcomes’. As a result, in February 2012, the technology was removed from the Prostheses List (now the Prescribed List of Medical Devices and Human Tissue Products [PL]).

In 2012, PASC considered application [1273](#) for this technology from Sanofi-Aventis Australia Pty Ltd (Genzyme is a fully owned subsidiary of Sanofi-Aventis); the Decision Analytic Protocol (DAP, now referred to as a PICO confirmation) was published but application [1273](#) did not progress further. At that time, PASC recalled a key concern raised by MSAC in consideration of application 1140 was the lack of studies reporting follow up over five years, and that this would not be addressed by the newly proposed application, which would rely on two-year follow up from the SUMMIT randomised controlled trial (RCT) (Saric et al. 2014). Five-year follow up is now available for the SUMMIT RCT (Brittberg et al. 2018).

**Table 2 Prior MSAC applications for surgical interventions to treat chondral and osteochondral lesions of the knee**

Application No.	Title of application	Meeting date(s)
<u>1140</u>	Matrix-induced Autologous Chondrocyte Implantation (MACI) and Autologous Chondrocyte Implantation (ACI)	<b>MSAC:</b> 02 December 2010
<u>1273</u>	Matrix-induced Autologous Chondrocyte Implant	<b>PASC:</b> 12-13 April 2012 Did not proceed
<u>1569</u>	Chitosan-based cartilage biomatrix implant (BST-CarGel), in conjunction with the marrow stimulation technique (microfracture), for repair of focal cartilage defects	<b>PASC:</b> 08 August 2019 <b>MSAC:</b> 28-29 July 2020
<u>1578</u>	Arthroscopic injection of a bioadhesive hydrogel implant (JointRep™), in conjunction with microfracture, for treatment of osteochondral defects of the knee	<b>PASC:</b> 08 August 2019 <b>MSAC:</b> 29-30 July 2021

Note: Applications 1569 and 1578 are for interventions to be used in conjunction with microfracture but consider the same patient population (focal lesions of knee cartilage) so are relevant to this application.

Source: MSAC application page, Department of Health and Aged Care, available at <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/application-page>

### ***Clinical claims***

The clinical claims proposed in the application are as follows:

- Matrix-assisted ACI is superior to microfracture for clinical effectiveness in the treatment of symptomatic chondral or osteochondral lesions  $\geq 2 \text{ cm}^2$  and  $< 20 \text{ cm}^2$  in size.
- Matrix-assisted ACI is non-inferior<sup>1</sup> to microfracture for safety in the treatment of symptomatic chondral or osteochondral lesions  $\geq 2 \text{ cm}^2$  and  $< 20 \text{ cm}^2$  in size.

No clinical claims were made in the application comparing matrix-assisted ACI with other potential interventions for treatment of chondral or osteochondral lesions such as osteochondral autografting (i.e. mosaicplasty or osteochondral autograft transplantation), osteochondral allografting, or conservative treatment.

## **PICO criteria**

### ***Population***

The proposed population for matrix-assisted ACI treatment is patients aged 18 to 55 years who have failed conservative treatment of symptomatic, International Cartilage Repair Society (ICRS) grade 3 or 4 chondral focal lesions that are  $\geq 2 \text{ cm}^2$  and  $< 20 \text{ cm}^2$  in size in an otherwise normal knee. The intervention is not appropriate for patients with rheumatoid or other inflammatory arthritic conditions, osteoarthritis, or unstable or mal-aligned joints, unless being concurrently corrected.

In complex joints such as the knee, articular cartilage decreases friction and distributes load during full range of movement while weight bearing. It is composed of hyaline cartilage consisting of a dense

<sup>1</sup> Confirmed in pre-PASC period, written communication from applicant, 05 March 2024.

extracellular matrix with a sparse distribution of chondrocyte (cartilage) cells. Unlike other tissues, articular cartilage does not have blood vessels, nerves or lymphatics and is nourished by diffusion from the synovial fluid, so articular cartilage has a limited ability to repair itself when damaged. Loss of articular cartilage is known as a chondral defect. When the damage occurs in a discrete location, surrounded by healthy tissue, it is referred to as a focal lesion. Chondral injury occurs in many joints, although, according to the application, the knee joint is the most common requiring medical intervention. Lesions can occur in the femoral condyles, the medial and lateral surfaces of the tibial plateau, and the inner surface of the patella.

Cartilage damage can be caused by a precipitating trauma (such as a sporting injury), arthritis (e.g. osteoarthritis and the downstream effects of rheumatoid arthritis) or other degenerative diseases such as osteochondritis dissecans. Cartilage damage can also occur from joint instability or abnormal loading of the joint from other musculoskeletal abnormalities.

Cartilage defects can be graded according to the ICRS) Grading System (grade 1 to 4), which takes into account the depth of the lesion in relation to the underlying subchondral bone. When lesions involve the subchondral bone (i.e. the bone is exposed or damaged; ICRS grade 4), they are referred to as osteochondral lesions. As cartilage is not innervated, defects are not necessarily symptomatic, and may be detected incidentally on magnetic resonance imaging (MRI) or arthroscopy. Patients with symptomatic cartilage defects, particularly grade 3 and 4 lesions, may suffer pain, effusion, locking of the joint or instability, which can significantly interfere with activities of daily living. Functional impairment can be equivalent to that of patients eligible for knee arthroplasty (Heir et al. 2010).

First line treatment of symptomatic chondral defects is conservative treatment, which can include non-steroidal anti-inflammatories, physiotherapy and corticosteroid injections. Where conservative treatment has failed, surgical options may be considered for patients with ICRS grade 3 and grade 4 lesions (Biant et al. 2015).

A lower age limit of 18 years and an upper age limit of 55 years was requested in the application, which is consistent with the Australian Register of Therapeutic Goods (ARTG) entry for OrthoACI (Table 4 in 'Intervention; Regulatory status' section). This also aligns with the age of the population in the primary clinical evidence (SUMMIT RCT). The application stated '68% of individuals over 55 years of age have radiographic evidence of osteoarthritis and focal cartilage lesions arising from wear and tear associated with aging', and that these patients require joint replacement where symptom management ceases to be effective. The assessment report for matrix-assisted ACI/ACI in 2010 (application 1140) also used an upper age limit of 55 years, stating this was 'due to disease progression', without further clarification.

In 2012, PASC noted that knee replacement surgery is predominantly performed in patients aged >55 years, and advised that data from the MBS and the Australian Orthopaedic Association National Joint Replacement Registry should be reviewed to assist in the identification of the age range of likely recipients of treatment with matrix-assisted ACI (DAP for application 1273). In 2020, PASC noted there is no reason to impose an upper age limit of 55, given many people in their 60s and 70s are active and would benefit from an intervention that would repair cartilage lesions (Ratified PICO for BST-CarGel, application 1569). However, the ARTG indication for OrthoACI and the SUMMIT trial population are restricted to patients ≤ 55 years of age.

The assessment report should address the applicability of matrix-assisted ACI to treat tibial and patellar lesions, given the SUMMIT RCT was restricted to femoral lesions (condyles and trochlea).

*PASC discussed the appropriateness of the upper age limit of 55 years. The applicant's clinical expert acknowledged the difficulty in defining an upper age limit, as there are some fit and active older patients who may be good candidates for the intervention but would be excluded by an upper age limit of 55 years, but 55 years aligned with the evidence base provided by the SUMMIT RCT.*

*The applicant's clinical expert also noted the proposed lower age limit of 18 years aligned with the SUMMIT RCT and would exclude younger patients with degenerative conditions such as osteochondritis dissecans, who would otherwise be eligible for ACI. The applicant's clinical expert also stated that long-term observational evidence is available to support use in patients younger than 18 years. PASC noted that while expanding the service to these patients may be assessed in the future, the proposed age range of 18 to 55 years is reasonable for the current assessment as it aligns with the RCT evidence and with consultation feedback from the Australian Knee Society that agreed with the proposed population. Therefore, PASC considered that the proposed population should be restricted to patients aged between 18 to 55 years.*

*PASC discussed whether the assessment should be limited to femoral lesions only, because the SUMMIT RCT did not include tibial or patellofemoral lesions. The applicant's clinical expert advised that symptomatic tibial lesions are uncommon (estimated at less than 5% of presentations), and there is yet-to-be published favourable observational evidence for patellofemoral lesions. PASC noted the lack of RCT evidence for lesions at other locations may be problematic. PASC stated that the assessment could include lesions at other locations but must present supporting evidence to show a benefit for lesions at such locations.*

*PASC noted the current standard of care for the proposed patient population differed according to lesion size, and therefore advised that the PICO population should include two lesion-size groups:*

- $2\text{ cm}^2$  to  $4\text{ cm}^2$
- $> 4\text{ cm}^2$  to  $< 20\text{ cm}^2$ .

*The rationale for this decision is outlined in the Comparator section of this document.*

## **Intervention**

Matrix-assisted ACI is a two-stage surgical intervention. The initial procedure is an arthroscopic biopsy that harvests healthy articular cartilage from the affected joint. In the case of OrthoACI, the harvested tissue is transferred to a dedicated facility in Perth, where the chondrocytes are isolated from the cartilage and expanded in vitro over a period of approximately five weeks. Once expanded, the chondrocytes are transported back to the hospital where they are implanted in a second surgery. Immediately prior to implantation, a supporting collagen matrix is trimmed to the appropriate size and seeded with the cultured chondrocytes. The matrix is then placed over the lesion and fixed in place with fibrin glue. The joint is then articulated through its full range of motion to confirm the scaffold will not be dislodged during normal movement.

Over time, the mechanisms used to prevent chondrocyte leakage from the lesion after implantation have evolved (Table 3). First generation ACI involved injecting a liquid suspension of expanded chondrocytes

into the lesion and preventing leakage by capping with a periosteal patch (ACI-P; indicating periosteum), which was typically harvested from the patient’s tissue around the proximal medial tibia. This approach led to adverse events associated with the patch such as graft hypertrophy, often requiring further procedures to remove the overgrowth. A second generation of the technique used a cap made of collagen or hyaluronan to contain the liquid cell suspension within the lesion, and this is sometimes referred to as ACI-C (indicating collagen cap).

The third generation of ACI uses a collagen matrix embedded with chondrocytes to retain the cells at the lesion (matrix-assisted ACI). The SUMMIT RCT used this technique, with chondrocyte expansion supplied by Genzyme Biosurgery (Cambridge, Massachusetts, USA). The applicant’s product, OrthoACI, is a chondrocyte expansion service that is also implanted using a collagen matrix.

A fourth generation of techniques is now emerging that do not involve the use a collagen matrix or cap.

**Table 3 Generations of chondrocyte delivery and retention techniques for ACI**

Generation of technique	Technique	Details	Applicant-proposed intervention	Included in Summary of Evidence table
First	ACI-P	periosteal patch secured with sutures to cover injected cell suspension	x	✓
Second	ACI-C	Collagen or hyaluronan cap secured with sutures or fibrin glue to cover injected cell suspension	x	✓
Third	matrix-induced <sup>a</sup> ACI <sup>b</sup>	collagen matrix/ membrane/ scaffold with embedded chondrocytes secured over lesion with fibrin glue	✓	✓
Fourth	e.g. spheroids, pellets	extracellular matrix secreted by chondrocytes adheres to cartilage within the lesion (i.e. scaffold-free)	x	x

ACI = autologous chondrocyte implantation.

a Alternative terminology includes matrix-assisted, -applied, or -guided.

b MACI® is now a registered trademark.

Source: adapted from Matsushita et al. 2023.

The 2010 assessment report for ACI/matrix-assisted (MSAC application 1140) assumed all generations of the technology at that time to be clinically similar. In the subsequent DAP for MACI (application 1273; October 2012), PASC determined it would not be appropriate to assume matrix-assisted ACI and ACI are clinically equivalent, and resolved the assessment report (which did not go ahead) should be limited to MACI.

The applicant intends to restrict the application to ACI implanted with a collagen scaffold/ membrane (i.e. matrix-assisted ACI), excluding earlier generations of ACI that used a periosteal or collagen patch (ACI-P and ACI-C), and also excluding later versions of ACI delivery technologies that do not use a collagen scaffold/membrane.<sup>2</sup>

<sup>2</sup> Pre-PASC, written communication from applicant, 05 March 2024.

The applicant confirmed that a single OrthoACI chondrocyte expansion service is sufficient to treat any size lesions (i.e. up to 20 cm<sup>2</sup>) or multiple lesions being treated in a single surgical episode.<sup>2</sup>

#### *Regulatory status*

Orthocell produces OrthoACI and is currently the only ACI provider in Australia. An excerpt from the ARTG entry for OrthoACI is shown in Table 4. The OrthoACI ARTG entry does not specify the use of any associated materials, but the application states the product is to be used with any resorbable collagen matrix and fibrin glue. The ARTG includes entries for such materials (see 'Costs of OrthoACI and associated materials' section for further details).

The OrthoACI ARTG entry states OrthoACI should be used 'in conjunction with rehabilitation', and that the information-for-use (IFU) document includes rehabilitation guides. The recovery protocol involves an extended period of restricted activities, including no full weight bearing for a number of weeks. Candidates for the procedure must be prepared to undergo extended periods of rehabilitation. The applicant has noted the recovery protocol for matrix-assisted ACI is similar to that for the comparator (microfracture), but is surgeon specific, and more variation in protocol would be observed across clinical practice than between surgical approaches.



**Table 4 Excerpt from the Public Summary for the OrthoACI ARTG Entry**

<p><b>Summary for ARTG Entry:</b> 289402 Cellular Therapies - Chondrocytes - T - Ortho-ACI - Orthocell Ltd - Suspension - Vial</p>
<p><b>Products:</b> Chondrocytes - T - Ortho-ACI <b>Product Type:</b> Cellular Therapies <b>Effective Date:</b> 23/09/2022</p>
<p><b>Dosage form:</b> Suspension <b>Route of administration:</b> Implant <b>Active ingredients:</b> Chondrocyte 2 million cells/mL</p>
<p><b>Therapeutic Indication</b> Ortho-ACI is indicated for use in treatment of cartilage lesions associated with the knee, patella and ankle in patients who meet the following criteria:</p> <ul style="list-style-type: none"> <li>- Patients with cartilage damage caused by trauma, wear or degradation including cartilage lesions associated with chondromalacia patella or osteochondritis dissecans; and</li> <li>- Patients with symptomatic articular cartilage defects, with an international cartilage repair society (ICRS) grade III or IV; and</li> <li>- Patients in the age range of 18-55 years.</li> </ul> <p>Precautions must be taken to mitigate the risks associated with acute traumatic lesions (subchondral oedema, effusion, haematoma, and haemarthrosis); and</p> <p>Ortho-ACI should be used in conjunction with rehabilitation - guides are available (Ankle, 10-IFU-16, or Knee/Patella, 10-IFU-17).</p>
<p><b>Specific Conditions</b> The Ortho ACI Risk Management Plan (RMP), Issue No. 3 (TR-042) (19 January 2017, Data Lock Point 18 August 2016), included with submission BA-2012-00010, and any subsequent revisions, as agreed with the TGA must be implemented in Australia. An obligatory component of the Risk Management Plan applicable to this therapeutic good is Routine Biovigilance. Routine Biovigilance includes the submission of Periodic Safety Update Reports (PSURs). The reports must meet the requirements for Periodic Safety Update Reports as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report. Each report must have been prepared within seventy calendar days of the data lock point for that report, as required by the European Medicines Agency's Guideline for PSUR's covering intervals up to 12 months (including intervals of exactly 12 months). Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.</p>

Source: Australian Register of Therapeutic Goods (ARTG), available at <https://www.tga.gov.au/resources/artg/289402>

*PASC discussed the development of the intervention and confirmed that the application is restricted to matrix-assisted ACI (third generation ACI technology). PASC noted that the intervention must be used with rehabilitation.*

*PASC noted the applicant's pre-PASC response confirmed that while OrthoACI is currently delivered in Australia using a porcine collagen matrix, it is not necessary to limit the collagen matrix used with ACI to a porcine source.*

### **Comparator(s)**

#### *Rationale for comparator proposed in application*

The application proposed microfracture as the sole comparator, on the basis it is the comparator in the majority of ACI trials (including the SUMMIT RCT). The applicant stated that microfracture is the most commonly used surgical approach in Australia to repair focal chondral or osteochondral defects of the

knee.<sup>3</sup> No evidence was provided to support this assertion, however MBS claims data indicate microfracture and drilling are more frequently claimed than MBS items likely to be used for other knee cartilage repair surgeries (Table 6 in section 'Utilisation of MBS items for other interventions').

Issues regarding the proposed comparator include (and are discussed in detail in following sections):

- The proposed population is patients with lesions sized  $\geq 2 \text{ cm}^2$  and  $< 20 \text{ cm}^2$ . Although, the MBS item for microfracture does not include any restrictions based on lesion size, guidance from a UK Consensus Paper and the applicant indicate that microfracture should not be used for lesions greater than  $4 \text{ cm}^2$ . Further, although the SUMMIT RCT included patients with lesions  $\geq 3 \text{ cm}^2$  and  $< 20 \text{ cm}^2$ , the mean lesion size was  $4.8 \text{ cm}^2$ . Therefore, microfracture may not be an appropriate comparator for larger lesions ( $>4 \text{ cm}^2$ ).
- Similarly, the key clinical evidence did not include small lesions ( $2\text{-}3 \text{ cm}^2$ ), which may impact the ability to provide an evidence based comparison of matrix-assisted ACI with microfracture for patients with lesions this size.
- The most recent PASC advice regarding the appropriate comparator for matrix-assisted ACI was primarily watchful waiting (conservative or no treatment followed by knee replacement surgery when indicated) or, secondarily, earlier partial or full knee replacement (DAP for application 1273). Application 1273 proposed stratification of the population by lesion size (i.e.  $\geq 2 \text{ cm}^2$  to  $4 \text{ cm}^2$ ; and  $> 4 \text{ cm}^2$ ) but that was not supported by PASC in that application.
- MSAC has expressed concern regarding the lack of evidence supporting that microfracture is safe and effective, noting any resubmission of JointRep (an injectable device added to microfracture) would need to present clinical trial evidence addressing the safety and effectiveness of microfracture alone (compared to placebo). The need for such a trial could be referred to the Medical Research Future Fund (MRFF) (Public Summary Document [PSD] for application 1578).

No Australian guidance was identified for the management of patients with symptomatic chondral lesions of the knee. In 2015, a UK Consensus Paper was published, facilitated by the British Association for Surgery of the Knee, on the surgical management of symptomatic articular cartilage lesions of the knee (Biant et al. 2015). It includes evidence-based, consensus recommendations for managing these defects where conservative treatment has failed.

For patients who remain symptomatic after conservative treatment, activity level and willingness to undergo rehabilitation are taken into consideration when deciding the most appropriate management strategy.

For patients who proceed to a knee cartilage surgery option, microfracture is the most frequently used marrow-stimulating technique, but other options include drilling and nanofracture. Small perforations are created in the subchondral bone at the lesion site using surgical awls, drill bits or other specialised instruments. The consequent bleeding from the bone marrow introduces stem cells into the lesion, which proliferate and generate new cartilage. The aim is to produce hyaline cartilage, but the technique can

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<sup>3</sup> Pre-PASC, written communication from applicant, 05 March 2024.

produce mostly fibrous cartilage (type I collagen), which has weaker biochemical and biomechanical properties than hyaline cartilage and is associated with poor long-term outcomes (Jareki et al. 2023).

There are alternative surgical options. Osteochondral autologous grafting aims to repair the lesion by transplanting cylinders of chondrocyte-bearing hyaline cartilage attached to subchondral bone sourced from an unaffected part of the joint, or another joint within the patient. This technique is appropriate for both chondral (e.g. grade 3) and osteochondral (i.e. grade 4) defects. There are two main approaches to osteochondral autografts: osteochondral autograft transplantation (OAT), which uses one or a few cylinders of osteochondral tissue; and mosaicplasty, which involves the grafting of multiple, small plugs (Medina and Görtz 2023).

For particularly large lesions, or where sufficient autograft tissue is unavailable, osteochondral cylinders may be sourced from a cadaver (osteochondral allograft).

Although an RCT comparing ACI with mosaicplasty (Bentley et al. 2012) has been listed by the applicant in the summary of evidence, the applicant has stated that this is for the sake of comprehensiveness. Despite this, the applicant does not propose mosaicplasty as a comparator, stating that it is not frequently used in Australia.<sup>4</sup>

The application did not discuss OAT or osteochondral allografting.

#### *Comparator by lesion size*

According to the UK Consensus Paper, where it has been decided to proceed with knee cartilage surgery, lesion size is the primary factor determining which surgical approach is most appropriate (Biant et al. 2015). The consensus recommendations for various lesion sizes are summarised in Table 5. Microfracture and similar regenerative interventions are recommended for symptomatic lesions < 2 cm<sup>2</sup>. However, these techniques may result in poor intermediate-term results for lesions between 2 cm<sup>2</sup> and 4 cm<sup>2</sup>, and should not be used for lesion > 4 cm<sup>2</sup> (Biant et al. 2015). The same recommendations apply to reconstructive interventions – mosaicplasty and OAT – with high donor site morbidity following OAT for lesions between 2 cm<sup>2</sup> and 4 cm<sup>2</sup> (Biant et al. 2015).

**Table 5 Consensus recommendations for knee cartilage repair or replacement from UK Consensus Paper**

<b>Cartilage surgery options</b>	<b>&lt; 2 cm<sup>2</sup></b>	<b>2 cm<sup>2</sup> to 4 cm<sup>2</sup></b>	<b>&gt; 4 cm<sup>2</sup></b>
Bone marrow stimulating techniques (e.g. microfracture)	✓	✓	
Osteochondral grafting (i.e. mosaicplasty, OAT)	✓	✓	
Cell therapy (i.e. ACI)		✓	✓
Osteochondral allograft transplantation			✓

OAT = osteochondral autograft transplantation.

Source: Adapted from Biant et al. 2015

As it is not recommended for lesions above 4 cm<sup>2</sup>, that the assessment group suggested that microfracture may not be an appropriate comparator for the entire proposed population of up to 20 cm<sup>2</sup>. Consistent with

<sup>4</sup> Pre-PASC, written communication from applicant, 05 March 2024.

this, the applicant stated that microfracture is indicated for lesions  $< 4 \text{ cm}^2$  in size,<sup>5</sup> and that in clinical practice, microfracture is very reluctantly used in large lesions.<sup>6</sup>

Stratifying the population according to the UK Consensus Paper recommendations would allow for different comparators for lesions of different size. The assessment group proposes:

- microfracture (main comparator) or conservative treatment for  $\geq 2 \text{ cm}^2$  and  $\leq 4 \text{ cm}^2$ , and
- conservative treatment for  $> 4 \text{ cm}^2$  and  $< 20 \text{ cm}^2$ .

It should be noted the SUMMIT RCT, which provides the primary clinical evidence, only included patients with lesions  $\geq 3 \text{ cm}^2$ . The mean lesion size across the RCT was  $4.8 \text{ cm}^2$  (range,  $3\text{-}20 \text{ cm}^2$ ; Saris et al. 2014), and findings were not stratified by lesion size. No comparative evidence has been listed by the applicant comparing ACI and microfracture for lesions between  $2 \text{ cm}^2$  and  $3 \text{ cm}^2$ .

#### *Prior advice for microfracture*

In 2010, expert clinical advice provided for the assessment report for matrix-assisted ACI/ACI (MSAC application 1140) suggested the decision to use one procedure over another is not always based on lesion size (p.12) and is influenced by clinician experience (p.13). The population was not stratified by lesion size in the assessment report. MSAC found that if matrix-assisted ACI/ACI were listed, it would substitute for some instances of microfracture, and that more evidence is needed to define the patient group likely to derive the most benefit from matrix-assisted ACI/ACI (PSD for application 1140).

In 2012, the DAP for matrix-assisted ACI (application 1273) considered two populations: patients with lesions  $\geq 2 \text{ cm}^2$  and  $\leq 4 \text{ cm}^2$ , and patients with lesions  $> 4 \text{ cm}^2$ . Application 1273 proposed that the most appropriate comparator for matrix-assisted ACI for patients with lesions sized between  $2\text{-}4 \text{ cm}^2$  was microfracture. For patients with lesions  $> 4 \text{ cm}^2$ , application 1273 stated there was no appropriate comparator as there are no treatments that are deemed effective in larger lesions other than matrix-assisted ACI. In relation to patients with lesions  $\geq 2 \text{ cm}^2$  and  $\leq 4 \text{ cm}^2$ , at that time PASC noted expert advice that in the absence of matrix-assisted ACI, some clinicians would prefer to manage this patient population by watchful waiting (with conservative management) rather than microfracture and determined that the clinical place for matrix-assisted ACI for this population was primarily in substitution of conservative management (DAP for application 1273, pp.15-16).

For patients with lesions  $> 4 \text{ cm}^2$ , at that time PASC noted clinical expert advice that microfracture produces significantly inferior results in this population. The proposed comparator of 'no treatment' was clarified as primarily watchful waiting (conservative or no treatment followed by knee replacement surgery when indicated), or, secondarily, earlier partial or full knee replacement (DAP for application 1273, p.16). Therefore, at that time PASC resolved that the appropriate comparator for matrix-assisted ACI (in patients with lesions sized  $2\text{-}4 \text{ cm}^2$  and patients with lesions sized  $>4 \text{ cm}^2$ ) was primarily watchful waiting (conservative or no treatment followed by knee replacement surgery when indicated) or, secondarily, earlier partial or full knee replacement.

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<sup>5</sup> Pre-PASC, written communication from applicant, 05 March 2024.

<sup>6</sup> Pre-PASC meeting with department and applicant, 19 February 2024.

The most recent advice from the UK National Institute for Health and Care Excellence (NICE) regarding appropriate comparators for knee cartilage defects are technology appraisals [TA477 \(2017\)](#) and [TA508 \(2018\)](#) for ACI. A number of comparators were listed, depending on defect size, and the committee noted variation across clinical practice due to the experience and preference of treating clinicians and the availability of treatment. Nonetheless, for both appraisals, the final scope listed microfracture as an appropriate comparator only for lesions up to 2 cm<sup>2</sup>, and best supportive care for lesions larger than 2 cm<sup>2</sup>.

More recent PASC advice regarding microfracture for this patient population is available in relation to MSAC applications for injectable bioscaffolds (BST-CarGel, application 1569; JointRep, application 1578). In August 2019, PASC confirmed that microfracture is an appropriate comparator for lesions  $\geq 2$  cm<sup>2</sup> for these injectable scaffolds, although it is relevant that the injectable bioscaffolds are designed to be used in conjunction with microfracture, whereas matrix-assisted ACI is intended to be used instead of microfracture.

In 2020, MSAC noted that the Evaluation-Sub-Committee (ESC) considered expert advice that indicated microfracture is appropriate for the treatment of knee cartilage lesions of up to 5 cm<sup>2</sup> (PSD for BST-CarGel application 1569). MSAC also noted that patient age and level of activity are important considerations that are 'equally as important as lesion size' when deciding on surgical approach, and that there is 'limited evidence that microfracture should be accepted as the gold standard for the treatment of chondral lesions of the knee'.

#### *Prior advice for mosaicplasty and other comparators*

The 2010 application for MBS services for ACI/matrix-assisted ACI (application 1140) used the term 'mosaicplasty' to refer to any type of osteochondral autografting. In 2010, MSAC found that if listed, matrix-assisted ACI/ACI would substitute for some instances of mosaicplasty and considered both mosaicplasty and debridement to be appropriate comparators alongside microfracture (application 1140). The PICO for the assessment report also listed osteochondral allografting as a potential comparator, but no comparative evidence was presented.

In 2012, PASC determined that mosaicplasty was not an appropriate comparator for patients with lesions  $\geq 2$  cm<sup>2</sup> and  $\leq 4$  cm<sup>2</sup> based on expert advice that in clinical practice it is infrequently used and is predominantly used in younger patients (DAP for application 1273). PASC also resolved that matrix-assisted ACI would not be used in place of debridement. Osteochondral allografting was not proposed by the applicant nor discussed by PASC.

The 2017 and 2018 NICE technology appraisals for ACI (TA477, TA508) determined that mosaicplasty is rarely used in National Health Service (NHS) clinical practice and so is not an appropriate comparator in the UK for any size lesions. Osteochondral allografting was not discussed.

In 2020, PASC noted clinical expert advice that mosaicplasty is rarely used in Australia because it is a technically difficult procedure to perform and agreed that it was therefore not a suitable comparator for BST-CarGel (application 1569). In 2021, PASC made a different decision in consideration of JointRep (application 1578), and mosaicplasty was selected as a comparator for patients with lesions  $\geq 2$  cm<sup>2</sup>, noting the inconsistency with the PICO for BST-CarGel.

Osteochondral allografting was not discussed in the Ratified PICO for either BST-CarGel or JointRep.

### Utilisation of MBS items for other interventions

In July 2021, MBS items for orthopaedic knee surgery were revised, and the existing knee arthroscopy items were replaced with nine new items, separated into three tiers based on complexity, to better reflect the range of complexity associated with arthroscopic procedures of the knee<sup>7</sup>. Recent claims data for MBS items used, or potentially used, for comparator services are tabulated below to provide potential upper limits to the current MBS-funded surgical interventions for knee cartilage lesions (Table 6).

MBS item 49576 is specific to microfracture or microdrilling for chondral lesions of the knee. There are no knee-specific MBS items for osteochondral autografting services, but a selection of four potentially suitable items are tabulated. Item 48251 would be appropriate for an osteochondral autologous grafting service (harvesting and insertion of osteochondral graft (autograft) via separate incisions at the same joint or joint complex), but is not knee specific, although it is likely such procedures are performed most frequently in knee joints. Alternatively, MBS items specific to the knee may be used, but the descriptors are broader (MBS item 49584) or include a number of procedures of which only one may relate to osteochondral autografting (MBS items 49503 or 49506).

**Table 6 Recent claims data for MBS items used, or potentially used, to claim services for alternative surgical options**

MBS item	Descriptor excerpt	Claims in 2022/2023
<b>Microfracture</b>		
49576	Repair of chondral lesion of knee, by arthroscopic means, including either or both of the following (if performed): (a) microfracture (b) microdrilling	1,581
<b>MBS items that may be appropriate for osteochondral autografting (including mosaicplasty)</b>		
48251	Harvesting and insertion of osteochondral graft (autograft) via separate incisions at the same joint or joint complex	71
49584	Chondral, osteochondral or meniscal graft of knee, by arthroscopic means	195
49503	Arthrotomy of knee, including one of the following: (e) repair or replacement of chondral or osteochondral surface (excluding prosthetic replacement)	231
49506	Arthrotomy of knee, including 2 or more of the following: (e) repair or replacement of chondral or osteochondral surface (excluding prosthetic replacement)	193

MBS = Medicare Benefits Schedule

Source: Services Australia Medicare item reports (accessed 27 September 2023)

### Comparators used in ongoing clinical trials

#### Microfracture

Most clinical trials of ACI have completed and used microfracture as a comparator. A cursory search identified three ongoing trials using microfracture as the comparator; one for a matrix-assisted ACI,<sup>8</sup> one

<sup>7</sup> Medicare Benefits Schedule Orthopaedic Surgery Items – Factsheet. ‘Changes to MBS Items for Orthopaedic Knee Surgery.’ Accessed on 04 March 2024 at [https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/F3E1DA9A21343EA6CA258646007893F7/\\$File/Factsheet-Knee%20.pdf](https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/F3E1DA9A21343EA6CA258646007893F7/$File/Factsheet-Knee%20.pdf).

<sup>8</sup> NCT01957722: NOVOCART®3D, completing in 2027.

for matrix-assisted ACI in patients aged 10-17 years,<sup>9</sup> and another for a fourth generation ACI that does not use a collagen scaffold.<sup>10</sup>

#### Mosaicplasty

The applicant listed one study of ACI versus mosaicplasty (Bently et al. 2012). A literature search identified another RCT comparing ACI with mosaicplasty (Clavé et al. 2016). At two-year follow up, this study found superior outcomes in the mosaicplasty group, although it should be noted the matrix used in this study was Cartipatch, which is a hydrogel scaffold, and the technique used in the ACI group was not representative of typical ACI procedures (Cook et al. 2016).

#### Osteochondral autograft transplantation

The applicant listed no studies that used OAT as a comparator. A literature search identified one RCT using this comparator and reporting two-year outcomes (Horas et al. 2003). Given this study was completed over twenty years ago, the ACI procedure used may not be representative of current generation ACI procedures.

#### Conservative management

An ongoing trial of matrix-assisted ACI (using Chondro Gide) versus debridement plus physiotherapy (NCT02636881<sup>11</sup>) is due to be completed in September 2024. The published protocol (Randsborg et al. 2016) describes the comparator as simple arthroscopic debridement and physiotherapy for osteochondral defects > 2 cm<sup>2</sup>, excluding patients with osteoarthritis. Debridement may be performed during diagnostic arthroscopy for cartilage lesions, prior to any decisions regarding surgical intervention, so this study may provide evidence for the alternative comparator of conservative treatment, once published.

*PASC noted that the nominated comparator was microfracture, which is currently MBS listed. PASC also noted that the last time MSAC considered an application for this indication (MSAC application 1578), microfracture was nominated as the comparator. However, at that time, MSAC concluded there was insufficient evidence that microfracture was safe and effective and that clinical trial evidence addressing the safety and effectiveness of microfracture alone versus placebo was required. PASC recalled that the most recent prior PASC advice was that the appropriate comparator for matrix-assisted ACI was watchful waiting (with conservative management) for all lesions > 2 cm<sup>2</sup> (PICO confirmation for MSAC application 1273). PASC also noted subsequent UK consensus guidance that recommends microfracture should not be used for lesions > 4 cm<sup>2</sup>.*

*The applicant's clinical expert noted the well-established natural history of steady decline in patients with symptomatic chondral lesions managed with watchful waiting, leading to joint degeneration, and that there is published Australian data regarding this. The clinical expert was of the opinion that microfracture harms the subchondral plate, which is an integral part of the osteochondral unit. For lesions of > 4 cm<sup>2</sup>, microfracture failure rates were described as high, noting surgeons are less inclined to use it for such large lesions. Therefore, in the absence of any good surgical alternatives for lesions > 4 cm<sup>2</sup>, clinicians tend to adopt watchful waiting despite the unsatisfactory outcomes for patients. The applicant's clinical expert considered there are no effective surgical comparators for the sub-population of patients with lesions*

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<sup>9</sup> NCT03588975: MACI®, completing in 2027.

<sup>10</sup> NCT05051332: CartiLife®, completing in September 2024.

<sup>11</sup> Accessed on 04 March 2024 at <https://clinicaltrials.gov/study/NCT02636881>.

*> 4 cm<sup>2</sup>. The applicant's clinical expert also noted that some patients in the SUMMIT RCT would have had multiple non-contiguous focal lesions, and therefore that not all patients reported as having a large total lesion area were treated for a single large lesion.*

*PASC asked the applicant whether it was known what proportion of presenting patients had lesions > 4 cm<sup>2</sup>. The applicant confirmed knowledge of an Australian publication reporting such data. The applicant's clinical expert stated the majority of matrix-assisted ACI-treated lesions in Australia are between 2 cm<sup>2</sup> and 4 cm<sup>2</sup>, with larger lesions typically progressing to joint replacement.*

*PASC advised that the population should include two subgroups based on lesion size with different comparators:*

- *2 cm<sup>2</sup> to 4 cm<sup>2</sup>, for comparison with microfracture*
- *> 4 cm<sup>2</sup> to < 20 cm<sup>2</sup>, for comparison with watchful waiting (with conservative treatment).*

*PASC noted there may be a lack of trial data for watchful waiting and therefore, the comparison of matrix-assisted ACI versus watchful waiting may have to be informed using observational data for the comparator of watchful waiting.*

*PASC noted that concerns about microfracture have been raised by MSAC and/or PASC each of the four times this indication has come before them. PASC noted that while MSAC had previously advised that an RCT of microfracture alone versus placebo should be undertaken to establish the benefit of microfracture, it appeared that no such trial has been undertaken. PASC advised the uncertainty in the safety and effectiveness of microfracture raised by MSAC may impact the evaluation of matrix-assisted ACI where microfracture is used as a comparator.*

## **Outcomes**

The outcomes proposed to assess the clinical claims are shown in Table 7. There are a number of knee-specific functional measures that are appropriate to establish the patient-relevant comparative benefits of ACI and comparator interventions. Rates of progression through the clinical pathway to total or partial knee arthroplasty will be an important outcome to inform the economic analysis.

The application classifies treatment failure as a safety outcome (harm), but it is classified herein as an efficacy outcome. Treatment failure may be variously defined: subsequent surgery to treat the index lesion; failure to achieve a pre-specified threshold for a functional or symptom measure; or a compound outcome of functional measures and/or pain measures and/or requirement for retreatment.

For example, treatment failure was a compound outcome in the SUMMIT RCT, defined as the following at any time after Week 24:

- the patient and physician global assessment result was the same as or worse than at baseline
- a <10% improvement in the KOOS pain subscale
- physician-diagnosed failure ruling out all other potential causes
- the physician deciding that surgical retreatment was needed.

Analyses should include responder analyses in addition to differences in mean change from baseline.



**Table 7 Proposed outcomes**

Outcome type	Outcome
Safety	Serious adverse events (e.g. arthralgia, cartilage injury, meniscus injury, development of osteoarthritis) Device-related adverse events (e.g. graft hypertrophy) Surgery-related adverse events (including additional general anaesthesia compared to comparators)
Patient-relevant effectiveness	Knee-specific functional measures such as: <ul style="list-style-type: none"> <li>• Knee Injury and Osteoarthritis Outcome Score (KOOS)</li> <li>• Lysholm Knee Score</li> <li>• Tegner Activity Level Scale</li> <li>• Cincinnati Knee Rating Score (CKRS)</li> <li>• International Knee Documentation Committee (IKDC) Subjective Knee Score</li> </ul> Other functional outcomes such as the 'Six-minute walk test' Quality-of-life measures such as EQ-5D and SF-36 Pain measures (e.g. VAS) Subsequent procedures: <ul style="list-style-type: none"> <li>• subsequent conservative treatment interventions to treat index lesion e.g. corticosteroid injections</li> <li>• subsequent surgery to treat index lesion (other than joint replacement)</li> <li>• rates of progression to joint replacement (i.e. total or partial knee arthroplasty)</li> </ul> Compound treatment failure outcomes using any of the above
Healthcare resources	Cost of ACI and associated materials (i.e. collagen matrix scaffold and fibrin glue). Cost of procedure (i.e. proposed service fee; anaesthetist services; theatre/admission costs, including consumables)

EQ-5D = EuroQuol Group 5-Dimension Self Report Questionnaire; ICRS = International Cartilage Repair Society; OAT = osteochondral autologous transplantation; SF-36 = Short Form-36; VAS = visual analog scale.

*PASC noted that there appear to be many types of potential adverse events associated with the intervention. PASC queried whether a particular demographic, such as older patients, were more likely to experience adverse events, noting that consultation feedback suggested greater effectiveness in younger patients with shorter duration of symptoms. The applicant's clinical expert advised that graft failure is the main adverse event, which is more likely in older patients, but that patient-related factors such as obesity and instability of the knee joint may also increase the risk of adverse events.*

*PASC agreed with the proposed outcomes.*

## Clinical management algorithms

According to the application, the referral pathways and clinical management of patients is the same prior to consideration of surgery to repair or replace focal cartilage lesions of the knee. Cartilage defects are definitively identified by medical imaging or arthroscopy, which both allow for the lesion size and grade to be assessed, along with the quality of the surrounding cartilage. The application stated imaging uses MBS item 63328 for MRI (scan of musculoskeletal system for derangement of knee or its supporting structures) and arthroscopy uses MBS item 49570 (Diagnosis of knee, by arthroscopic means, when the pre-procedure diagnosis is undetermined, including either or both of the following (if performed): biopsy; lavage). According to the application, debridement may also be performed during this initial diagnostic procedure.

First-line treatment is conservative treatment, which includes rest, non-steroidal anti-inflammatories and physiotherapy. Other non-operative therapies for more severe symptoms may include corticosteroid injections, viscosupplementation (injection of lubricating fluid, typically hyaluronic acid, into the knee joint) or an unloading brace. The application noted these interventions may address symptoms but will not contribute to healing the underlying defect. No accepted definition of conservative treatment was identified.

In the absence of Australian or other clinical guidelines for the management of symptomatic articular cartilage lesions of the knee, the UK Consensus Paper (Biant et al. 2015) was used to inform the clinical algorithms in Figure 1 and Figure 2.

Where response to conservative treatment is poor, patients would be considered for surgical intervention if the lesions are ICRS grade 3 or 4. For small lesions ( $< 2 \text{ cm}^2$ ), microfracture is the recommended treatment; these lesions do not appear in the clinical algorithm shown below, which is restricted to lesion sizes of relevance to this application (i.e.  $\geq 2 \text{ cm}^2$  and  $< 20 \text{ cm}^2$ ).

According to the PSD for MSAC application 1140 for ACI/matrix-assisted ACI, ACI is used in the Australian setting as a first-line surgical treatment following failure of conservative therapy to improve the condition. MSAC noted expert opinion that matrix-assisted ACI implants are performed overseas as a second-line surgical procedure after failed microfracture. The current application (1773) indicated that while ACI can be performed after microfracture, it was suggested that outcomes are better if ACI is used prior to the damage caused by marrow-stimulating techniques. The study publications for the SUMMIT RCT do not state whether any subjects had received microfracture prior to study enrolment.

The selection of microfracture for lesion  $\geq 4 \text{ cm}^2$  is shown as a dotted line in the clinical algorithms, in light of the general consensus that this surgical approach has poorer outcomes in these sized lesions (UK Consensus Paper; Biant et al. 2015), and advice from the applicant that microfracture is very reluctantly used in large lesions.<sup>12</sup>

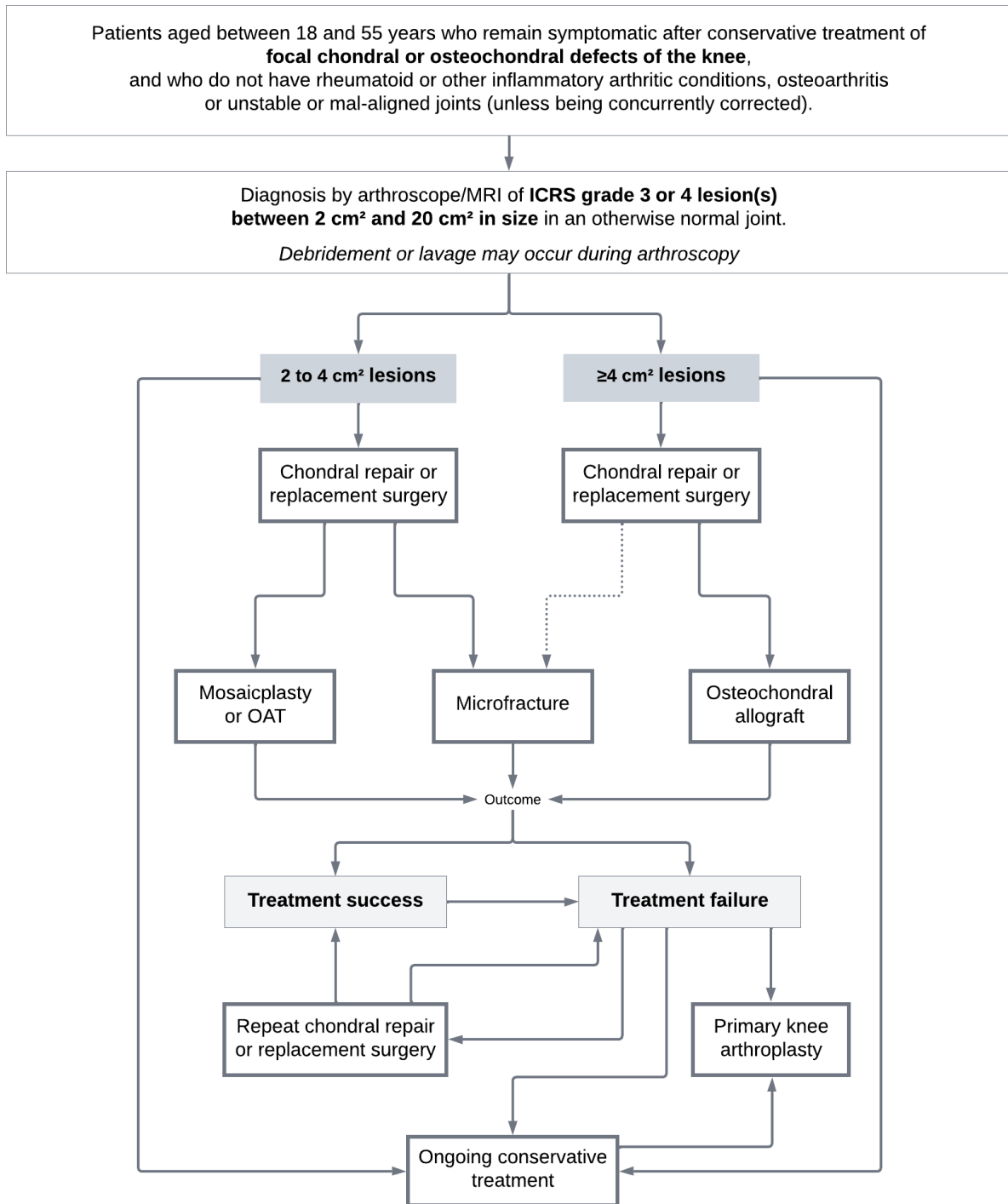
As surgical approaches are not always durable, patients may progress to treatment failure after an initially successful surgery. These patients may go on to receive primary knee arthroplasty or return to further conservative treatments to manage symptoms.

In the clinical algorithms shown below, primary arthroplasty may also occur without chondral repair or replacement surgery (i.e. via ongoing conservative management). The application suggested that joint replacement may be required when patients reach the age of 55 years or older. However, it should be noted that some patients within the proposed population may progress to primary knee arthroplasty sooner, for example older patients (within the proposed population) with larger lesion(s) causing significant pain and loss of function.

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<sup>12</sup> Pre-PASC meeting with department and applicant, 19 February 2024.

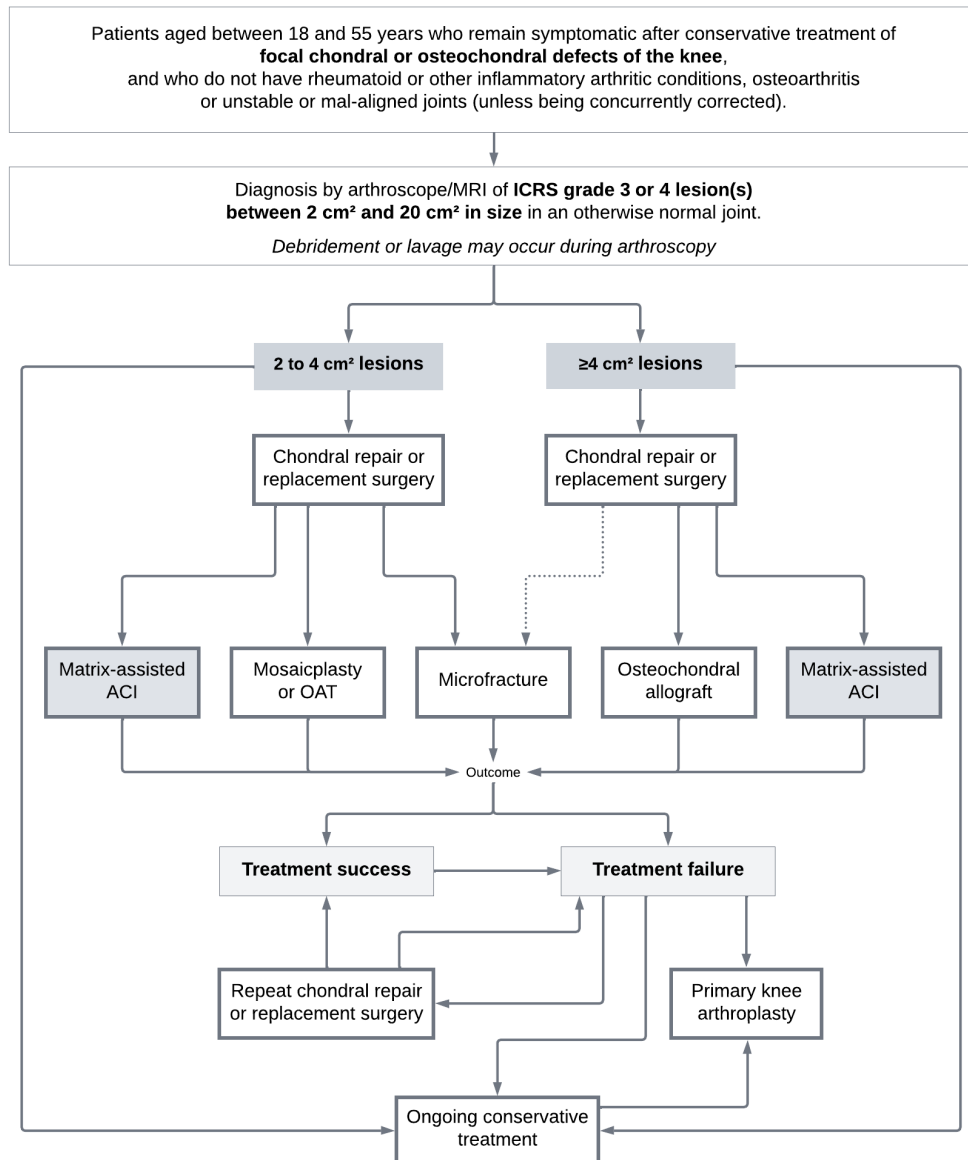
**Figure 1 Clinical management algorithm without proposed service**



ACI = autologous chondrocyte implantation; ICRS = International Cartilage Repair Society; MRI = magnetic resonance imaging; OAT = osteochondral autograft transplantation.

Note: Dotted line indicates intervention may not be appropriate for this population.

**Figure 2 Clinical management algorithm with the proposed service**



ACI = autologous chondrocyte implantation; ICRS = International Cartilage Repair Society; MRI = magnetic resonance imaging; OAT = osteochondral autograft transplantation.

Note: Dotted line indicates intervention may not be appropriate for this population.

*PASC reviewed the clinical algorithms and noted that while ongoing conservative management was placed at the bottom, it is depicted as a comparator to chondral repair/replacement surgery. PASC did not request any changes.*

## Proposed economic evaluation

In light of advice from PASC and the applicant, the appropriate clinical claims would be:

- With regard to clinical effectiveness for the treatment of symptomatic chondral or osteochondral lesions, matrix-assisted ACI is
  - superior to microfracture for lesions from 2 cm<sup>2</sup> to 4 cm<sup>2</sup> in size, and

- superior to watchful waiting (with conservative treatment) for lesions > 4 cm<sup>2</sup> to < 20 cm<sup>2</sup> in size.
- With regard to safety in the treatment of symptomatic chondral or osteochondral lesions, matrix-assisted ACI is
  - non-inferior to microfracture for lesions from 2 cm<sup>2</sup> to 4 cm<sup>2</sup> in size, and
  - non-inferior to watchful waiting (with conservative treatment) for lesions > 4 cm<sup>2</sup> to < 20 cm<sup>2</sup> in size.

On the basis of these clinical claims, the appropriate economic analysis would be a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) (Table 8).

**Table 8 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation**

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain <sup>a</sup>	Noninferior <sup>b</sup>	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain <sup>a</sup>	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior <sup>b</sup>	Health forgone: need other supportive factors	?	CMA	<b>CEA/CUA</b>
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis.

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations.

b An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence.

The five-year follow up of the SUMMIT RCT (Brittberg et al. 2018) of matrix-assisted ACI versus microfracture is the main comparative evidence that would support a claim of superiority. Inclusion criteria included a lesion size of ≥ 3 cm<sup>2</sup>. No additional comparative studies have been listed by the applicant that provide evidence for patients with lesions ≥ 2 cm<sup>2</sup> and < 3 cm<sup>2</sup>; therefore, the evidence and proposed population may not completely align.

The mean lesion size in the SUMMIT RCT was 4.8 cm<sup>2</sup> and ranged from 3 to 20 cm<sup>2</sup> (Saris et al. 2014).

Published findings are not reported by lesions size subgroups (e.g. ≥ 2 cm<sup>2</sup> and ≤ 4 cm<sup>2</sup>), and microfracture may not be the appropriate comparator for lesions > 4 cm<sup>2</sup> (as discussed in the Comparator(s) section).

A cost-effectiveness analysis (Aae et al. 2018) found that ACI was not cost effective compared to microfracture. However, the included studies were not limited to matrix-assisted ACI and were likely to be mostly earlier generation ACI given only studies with five-year follow up were eligible for inclusion.

*PASC confirmed that a CUA or CEA would be appropriate for a clinical claim of superiority. PASC noted that the SUMMIT RCT only included patients with lesions  $\geq 3 \text{ cm}^2$  and  $< 20 \text{ cm}^2$ , and that no further clinical evidence demonstrating the effectiveness and safety of matrix-assisted ACI compared to microfracture for lesions between  $2 \text{ cm}^2$  and  $3 \text{ cm}^2$  had been provided.*

## **Proposal for public funding**

The application proposed two new MBS items; one for harvesting the cartilage biopsy (from which the chondrocytes are extracted) and another for a subsequent procedure to implant the expanded chondrocyte culture. According to the applicant, arthrotomy is typically used for the implantation procedure, although some surgeons use an arthroscopic approach.<sup>13</sup> The application stated both the harvesting and implantation procedures are inpatient, day surgeries. According to the application, ACI must be performed by an orthopaedic surgeon who has undergone Orthocell Ltd training in the use of OrthoACI. The supply of OrthoACI is restricted to relevant medical professionals who have completed the training program. Training consists of a presentation delivered by Orthocell Ltd representatives to provide initial familiarisation with the product and processes.

### ***Proposed MBS item and fee for harvesting procedure***

The application proposed an item descriptor for the harvesting procedure; this has been modified in the proposed new MBS item (Table 9) to match the population developed for this PICO confirmation (shown using blue text/strikethrough).

The application proposed a fee of \$849.45 for the proposed cartilage harvesting item and referenced the MBS item 49584 (arthroscopic grafting; fee: \$853.70). MBS item 49584 is for complex arthroscopic procedures (Table 10)<sup>14</sup> however, the application did not provide further information to justify that the proposed procedure is of the same complexity and time as MBS item 49584. Therefore, the proposed fee would need to be justified in the assessment report in terms of the length of time and complexity of the procedure. The application described the harvest procedure as an arthroscopic biopsy, so MBS item 49570 (arthroscopic biopsy; fee: \$300.45, Table 10) may be a more appropriate guide for the proposed fee.

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<sup>13</sup> Pre-PASC, written communication from applicant, 05 March 2024

<sup>14</sup> This is a Tier 3 MBS item; Tier 3 items are for complex knee arthroscopic services.

**Table 9 Proposed MBS item descriptor and fee for the chondrocyte harvesting procedure**

<p>Category 3 – Therapeutic Procedures                  Group T8 – Surgical Operations                  Subgroup 15 – Orthopaedic                  Subheading – 12 Knee</p>
<p>MBS item XXXX</p> <p><i>Arthroscopic harvesting of cartilage of knee for preparation of Autologous Chondrocytes Implantation – where patients are aged between 15-55 years; <del>have a focal chondral defect which is <math>\geq 2\text{cm}^2</math>; and have one or more symptomatic focal chondral or osteochondral defects of the knee that are</del></i></p> <ul style="list-style-type: none"> <li>• <i>at least 2 cm<sup>2</sup> but smaller than 20 cm<sup>2</sup> in size in an otherwise normal joint</i></li> <li>• <i>ICRS grade 3 or 4</i></li> </ul> <p><i>and who do not have rheumatoid or other inflammatory arthritic conditions, osteoarthritis or unstable or mal-aligned joints, unless being concurrently corrected.</i></p> <p><i>First of two surgical procedures, with subsequent in vitro culture expansion and chondrocyte implantation.</i></p> <p><i>Multiple Operation Rule</i></p> <p><i>(H)</i></p> <p><i>(Anaes.) (Assist.)</i></p>
<p>Proposed Fee: \$853.70      Benefit: 75% = \$640.30</p>

Note: text is applicant's proposed MBS item, Italics and strikethrough indicates suggested edits by the assessment group.

**Table 10 MBS items to support fees for proposed service for chondrocyte harvesting**

MBS item	Descriptor	Benefit
<b>MBS item proposed by applicant to support fee</b>		
49584	Chondral, osteochondral or meniscal graft of knee, by arthroscopic means (H) Multiple Operation Rule (Anaes.) (Assist.)	Fee: \$853.70 Benefit: 75% = \$640.30
<b>Alternative MBS item to support fee</b>		
49570	Diagnosis of knee, by arthroscopic means, when the pre-procedure diagnosis is undetermined, including either or both of the following (if performed): (a) biopsy; (b) lavage (H) Multiple Operation Rule (Anaes.) (Assist.)	Fee: \$300.45 Benefit: 75% = \$225.35

Source: MBS online, Department of Health and Aged Care, accessed March 2024 at <https://www9.health.gov.au/mbs/search.cfm>

***Proposed MBS item and fee for implantation procedure***

The second procedure – implantation of the cultured chondrocytes – is most often performed with mini-arthrotomy in Australia,<sup>15</sup> and is the technique used in the SUMMIT RCT.

<sup>15</sup> Pre-PASC, written communication from applicant, 05 March 2024.

The applicant proposed a single item descriptor for the implantation procedure by arthrotomy; this has been modified in the proposed new MBS item (Table 11) to match the population developed for this PICO confirmation and allow a choice of surgical approach.

The applicant proposed the fee for MBS item 49503 (arthrotomy of knee for repair or replacement of chondral or osteochondral surface; fee: \$538.90) would be appropriate for the proposed chondrocyte implantation procedure (Table 11). This appears to be a reasonable basis for the proposed fee. However, the proposed fees for the implantation service would need to be justified in the assessment report in terms of the length of time and complexity of the procedures.

**Table 11 Proposed MBS item descriptor and fee for the chondrocyte implantation procedure**

Category 3 – Therapeutic Procedures Group T8 – Surgical Operations Subgroup 15 – Orthopaedic Subheading – 12 Knee	
MBS item YYYY <del>Arthrotomy or arthroscopy of knee, including implantation of autologous chondrocyte graft where patients are aged between 15-55 years; – have a focal chondral defect which is <math>\geq 2\text{cm}^2</math> for implantation of autologous cultured chondrocytes on a collagen membrane in patients aged between 18 and 55 years with one or more symptomatic focal chondral or osteochondral defects of the knee that are:</del> <ul style="list-style-type: none"> <li>• <i>at least 2 cm<sup>2</sup> but smaller than 20 cm<sup>2</sup> in size in an otherwise normal joint</i></li> <li>• <i>ICRS grade 3 or 4</i></li> </ul> <i>and who do not have rheumatoid or other inflammatory arthritic conditions, osteoarthritis or unstable or mal-aligned joints, unless being concurrently corrected.</i> <i>Second of two surgical procedures, subsequent to autologous chondrocyte harvesting and expansion by in vitro culture.</i> <i>Applicable once per episode of care (for one or more lesions).</i> <i>Multiple Operation Rule</i> <i>(H)</i> <i>(Anaes.) (Assist.)</i>	
Proposed fee: \$538.90	Benefit: 75% = \$404.20

Note: Text is applicant’s proposed MBS item, Italics and strikethrough indicates suggested edits by the assessment group.

The applicant also stated implantation is increasingly being achieved with arthroscopy.<sup>16</sup> This is more technically challenging than implantation with arthrotomy, but results in a shorter hospital stay and fewer post-operative complications. A single item allowing both surgical approaches would be consistent with the principle of approach-agnostic MBS items for surgical procedures endorsed by the MBS Review Taskforce.

The MBS item structure for knee arthroscopy, revised in 2021, is stratified into three tiers depending on the complexity of the procedure.<sup>17</sup> Tier one covers basic diagnostic arthroscopy (item 49570; fee: \$300.45);

<sup>16</sup> Pre-PASC, written communication from applicant, 05 March 2024.

<sup>17</sup> Medicare Benefits Schedule Orthopaedic Surgery Items – Factsheet. ‘Changes to MBS Items for Orthopaedic Knee Surgery.’ Accessed on 04 March 2024 at



Tier two covers medium complexity arthroscopy (items 49572, 49574, 49576, 49578 and 49580; fee: \$731.15); and Tier three covers complex knee arthroscopy (items 49582, 49584 and 49586; fee \$853.70). The application listed the appropriate Australian refined diagnosis-related groups (AR-DRG) for the implantation procedure as 'Arthroscopy, Minor Complexity' (p.21 of the application). On that basis, if a second MBS item were to be considered for arthroscopic implantation, the appropriate fee may be that for a Tier two knee arthroscopy. An example of a Tier two knee arthroscopic service is Item 49576 used to claim microfracture services (Table 12).

**Table 12 MBS items to support fees for proposed service for chondrocyte implantation**

MBS item	Descriptor excerpt	Benefit
<b>MBS item proposed by applicant to support fee for implantation by arthrotomy</b>		
49503	Arthrotomy of knee, including one of the following: (a) meniscal surgery; (b) repair of collateral or cruciate ligament; (c) patellectomy; (d) single transfer of ligament or tendon; <b>(e) repair or replacement of chondral or osteochondral surface</b> (excluding prosthetic replacement); other than a service associated with a service to which another item in this Group applies	Fee: \$538.90 Benefit: 75% = \$404.20
<b>MBS items that could support fee for an arthroscopic implantation service</b>		
49576	Repair of chondral lesion of knee, by arthroscopic means, including either or both of the following (if performed): (a) microfracture; (b) microdrilling; other than a service performed in combination with a service to which another item of this Schedule applies if the service described in the other item is for the purpose of performing chondral or osteochondral grafts	Fee: \$731.15 Benefit: 75% = \$548.40

Source. MBS online, Department of Health and Aged Care, accessed March 2024 at <https://www9.health.gov.au/mbs/search.cfm>

### **Number of services claimable**

The applicant proposed that more than one lesion can be treated simultaneously within a single joint as part of the single episode of care, with no additional costs associated with the chondrocyte expansion service. The applicant also proposed that patients who subsequently incur a new lesion in either the same knee or other knee should be eligible for an additional MBS service and has not proposed a limit to the number of times the service can be claimed by a patient.<sup>18</sup>

The applicant has not proposed a limit to the number of times the service can be claimed for a particular lesion, noting that if treatment fails, some patients may undergo a second procedure to repair the same lesion.<sup>19</sup> According to the applicant, if the second repair also fails, patients generally do not have any further ACI procedures for that lesion, instead returning to conservative treatment or proceeding to partial

[https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/F3E1DA9A21343EA6CA258646007893F7/\\$File/Factsheet-Knee%20.pdf](https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/F3E1DA9A21343EA6CA258646007893F7/$File/Factsheet-Knee%20.pdf).

<sup>18</sup> Pre-PASC, written communication from applicant, 05 March 2024.

<sup>19</sup> Pre-PASC, written communication from applicant, 05 March 2024.

or total knee replacement.<sup>20</sup> However, the application did not appear to provide any evidence on patients receiving repeat procedures.

When considering the 2012 DAP (MSAC application 1273), PASC advised the following regarding the number of times the item could be claimed under the MBS:

‘...the suggested listing could be expanded to allow for repeat and additional procedures however, if the listing were expanded to permit more than one service per patient per lifetime, then the application should also present evidence of effectiveness of repeat or additional matrix-assisted ACI procedures. Furthermore, the cost-effectiveness analysis would need to be adjusted to include the costs and benefits of repeat or additional matrix assisted ACI procedures. Alternatively, if the applicant considers that the risk of a repeat or additional MACI in a patient is so low that it should be considered negligible then the application should present evidence (e.g. from a registry) demonstrating the rate of repeat or additional matrix-assisted ACIs in patients having had matrix-assisted ACI.’

### ***Prescribed List of Medical Devices and Human Tissue Products***

OrthoACI and analogous technologies from other sponsors were originally listed on Part B of the PL, prior to de-listing after the MSAC decision in 2010 to no longer fund the harvesting and implantation services (MSAC application 1140 for ACI/matrix-assisted ACI). The applicant noted OrthoACI is currently the only ACI product manufactured in Australia, and that there are no similar products used in Australia. No other ACI products are currently listed on the ARTG.

The applicant has not lodged an application to re-instate the device on the PL; the application stated that ‘should the procedure be included on the MBS and the implant subsequently included on the Prostheses List, it will become more accessible for patients with private health insurance.’

Recent reform activities for Part B of the PL have proposed that items involving autologous tissues should not be listed, based on the view that such products represent a therapeutic process rather than a manufacturing one.<sup>21</sup> Prior and current PL Guidance material does not mention autologous tissues. Only three items are currently listed on Part B for autologous tissue items; two associated with services for skull caps (Billing Code MVS23; RNB02), and one for ‘Autologous Bone (Not Processed) (Billing Code QBB60)’. Any future applications for inclusion of OrthoACI on Part B of the PL would require justification that the price of the service reflects cost recovery in order to comply with the Human Tissue Act, which precludes profit from trade in human tissue.

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<sup>20</sup> Pre-PASC, written communication from applicant, 05 March 2024

<sup>21</sup> Prostheses List Reforms – Consultation Paper No 2(a) ‘Modernisation of Part B of the Prostheses List’. Published February 2022 by the Australian Department of Health and Aged Care. Accessed on 11 March 2024 at [https://consultations.health.gov.au/technology-assessment-access-division/consultation-paper-2a-modernising-of-part-b-of-the/supporting\\_documents/Consultation%20Paper%20No%20a%20%20Modernisation%20of%20Part%20B%20of%20the%20Prostheses%20List%20FINAL.pdf](https://consultations.health.gov.au/technology-assessment-access-division/consultation-paper-2a-modernising-of-part-b-of-the/supporting_documents/Consultation%20Paper%20No%20a%20%20Modernisation%20of%20Part%20B%20of%20the%20Prostheses%20List%20FINAL.pdf)

### **Costs of OrthoACI and associated materials**

The costs associated with the chondrocyte expansion service and associated materials for implantation procedure are listed in Table 13. OrthoACI is not currently listed on the PL. The collagen matrix currently used to contain the expanded chondrocytes is Chondro Gide - Orthopaedic cartilage repair membrane (ARTG 146887; Geistlich Pharma Australia Pty Ltd), although the application noted any resorbable collagen membrane approved for use in cartilage repair may be used. Chondro Gide is not listed on the PL.

The matrix is secured to the tissue around the lesion with a fibrin glue. The application did not specify a particular fibrin glue product, but the DAP for application 1273 for matrix-assisted ACI in 2012 nominated Tisseel VH S/D (frozen) fibrin sealant syringe (ARTG number 147141; Baxter Healthcare Pty Ltd) as a related device. As part of the PL reforms, this product was moved to Part D of the PL on 1 July 2023, along with a number of other 'General Use Items' used in a broad range of surgeries.

**Table 13 Costs of chondrocyte expansion service and associated materials for implantation procedure**

<b>Product</b>	<b>ARTG No.</b>	<b>Cost</b>	<b>Listed on PL?</b>	<b>PL application pending?</b>
<b>Chondrocyte expansion service</b>				
Chondrocytes - T - Ortho-ACI	289402	\$ REDACTED <sup>a</sup>	No	No
<b>Collagen matrix</b>				
Chondro Gide - Orthopaedic cartilage repair membrane	146887	\$880 <sup>a</sup>	No	No
<b>Fibrin glue</b>				
TISSEEL VH S/D fibrin sealant syringe	147141	\$323	BX214 Currently in Part D	N/A

ARTG = Australian Register of Therapeutic Goods; DAP = Decision Analytic Protocol; N/A = not applicable; NR = not reported; PL = Prescribed List of Medical Devices and Human Tissue Products.

<sup>a</sup> Provided by application.

Source: Application 1773 and Part D of the Prescribed List of Medical Devices and Human Tissue Products, accessed on 21 March 2024 at <https://www.health.gov.au/resources/publications/prescribed-list-of-medical-devices-and-human-tissue-products>

As the chondrocyte expansion service and the collagen matrix are not included on the PL, if the intervention was MBS listed, the costs for the chondrocyte expansion service and the collagen matrix (i.e. ~\$ REDACTED) may be borne as out-of-pockets costs by the patient.

The applicant confirmed that, where more than one discreet focal lesion is being treated in the same or contralateral knee, there will be no additional charge for the chondrocyte expansion service. Similarly, treatment for larger lesions will incur the same costs for chondrocyte expansion as small lesions.<sup>22</sup>

According to the applicant, there are currently approximately 40 ACI procedures performed in Australia annually, and most of these are performed on lesions of the knee. In the private sector the procedure is self-funded by patients or workers' compensation, and in the public sector it is funded by the hospital.

<sup>22</sup> Pre-PASC, written communication from applicant, 05 March 2024.

*PASC confirmed the proposed MBS item for implantation does not need to specify that the collagen matrix consists of porcine collagen.*

*PASC considered the addition of restrictions to the population description in the proposed MBS items for harvesting and implanting was appropriate.*

*PASC noted that repair of multiple lesions can be undertaken simultaneously and that a second repair of a lesion can be undertaken. However, the applicant's clinical expert advised that generally patients do not have further repairs. PASC considered that the number of services claimable did not need to be limited but noted a multiple operations rule needed to be added to the item descriptor.*

*PASC noted the proposed fee (\$853) for the harvesting procedure was based on MBS item 49584 (arthroscopic grafting) which is higher than the \$300.45 fee for MBS item 49570 for an arthroscopic knee biopsy procedure. PASC queried the justification for referencing the harvesting procedure fee against a complex arthroscopic grafting procedure. The applicant advised this was based on clinician advice. PASC advised that the assessment would need to provide some justification for the fee, perhaps drawing on the SUMMIT RCT which may discuss or report the duration of the procedure. PASC advised that the applicant developed assessment report (ADAR) needs to justify the proposed fee for both proposed MBS items in terms of factors such as the complexity of the procedure and expected procedure time, or where this justification is unavailable, align the fee with current comparable procedures.*

*PASC agreed with the suggested edits to the proposed MBS item descriptor for the implantation procedure to allow for implantation with either arthroscopy or arthrotomy.*

*PASC raised concerns regarding the potential for equity and accessibility issues arising from out-of-pocket costs associated with the intervention. It was noted rehabilitation protocols have advanced quite considerably over the last 10-15 years and are accelerated compared to what they used to be. The applicant's clinical expert advised that while rehabilitation periods are a little longer for ACI procedures compared to microfracture, they are not dissimilar in timeframe or costs, and are less costly than knee arthroplasty. PASC advised that the ADAR needs to clarify the magnitude of out-of-pocket costs associated with the prolonged rehabilitation times in both the matrix-assisted ACI and microfracture procedures.*

## **Summary of public consultation input**

*PASC noted and welcomed consultation input from one organisation. The one organisation that submitted input was:*

- Australian Knee Society (AKS).

The consultation feedback received was supportive.

### **Clinical need and public health significance**

The main benefits of public funding received in the consultation feedback included shorter duration of symptoms and the service providing an additional option for surgeons to treat small to medium sized chondral lesions, especially in younger patients. However, input indicated that this therapy could add cost

due to the requirement for two operations, an initial biopsy followed by an insertion procedure, compared to available options of microfracture or mosaicplasty.

Physiotherapy as a part of a rehabilitation program was identified as being needed to be delivered before or after the intervention.

### **Indication(s) for the proposed medical service and clinical claim**

The consultation feedback supported the proposed patient population with small chondral lesions.

The consultation feedback agreed with microfracture as the comparator for the proposed service.

The consultation feedback supported the clinical claim, noting sufficient published data as evidence to support the application.

### **Cost information for the proposed medical service**

The consultation feedback agreed with the service descriptor.

Input from the Australian Knee Society agreed with the service fee, noting it in line with the current fee for arthroscopic microfracture.

### **Consumer Feedback**

*PASC noted that consultation feedback was received from the AKS. While the feedback was supportive, the AKS noted declining use of matrix-assisted ACI over the past 10 years due to removal of the product from the PL. The AKS also stated that clinical outcomes are better in younger patients with shorter duration of symptoms and that the benefit is more durable compared to microfracture or mosaicplasty.*

## **Next steps**

*PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.*

*PASC noted the applicant has elected to progress its application as an ADAR (Applicant Developed Assessment Report).*

## **Applicant Comments on Ratified PICO**

The applicant wishes to make the following comments:

1. With respect to previous advice from MSAC that an RCT of microfracture alone versus placebo. should be undertaken to establish the benefit of microfracture. The applicant considers such a trial would be a sham surgery trial that would be unethical and inherently high risk. The applicant considers placebo-controlled trials are not appropriate for interventions requiring surgery. Practically, recruitment of such a trial would be highly difficult, if not impossible. We are concerned that reliance on this flawed recommendation places an unreasonable burden of proof on any applicant seeking to use microfracture to establish efficacy of any cartilage repair procedure through the MSAC process, especially since there are limited therapeutic options available. Microfracture has an MBS item number. The MBS Review has concluded that

microfracture has a place on the MBS. The onus should not be on the applicant to establish the safety and efficacy of a procedure that remains on the MBS following the lengthy and comprehensive MBS Review.

2. OrthoACI is not regulated under the Human Tissues Act, but under the Therapeutic Goods Act, classified as a Class 3 biological therapy. Consequently, OrthoACI does not fit comfortably in Part B of the PL, which is intended to cover mainly donated tissue and almost exclusively Class 2 biologicals. The applicant is aware of reforms to Part B of the PL which propose 3 different assessment pathways to evaluate human cell and tissue products for inclusion on the PL. The applicant believes that these reforms will clarify reimbursement for OrthoACI and other similar cell therapy products in the future, which will improve accessibility to patients while appropriately compensating manufacturers of such products.

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