Washington State Health Care Authority

November 15, 2024 Meeting Materials
Health Technology Clinical Committee

Previous meeting business

Contents

Washington State Health Care Authority

Health Technology Clinical Committee

Date: September 20, 2024
Time: 8:00 a.m. – 1:00 p.m.
Location: Webinar
Adopted: Pending

Meeting materials and transcript are available on the **HTA website.**

HTCC Minutes

Members present: John Bramhall, MD, PhD; Clinton Daniels, DC, MS; Chris Hearne, DNP, MPH; Conor Kleweno, MD; Evan Oakes, MD, MPH; Sheila Rege, MD; Tony Yen, MD
Clinical experts: Michael James, MD

HTCC Formal Action

1. **Welcome and Chair remarks:** Dr. Rege, chair, called the meeting to order; members present constituted a quorum.
2. **HTA program updates:** Josh Morse, program director, presented HTCC meeting protocols and guidelines, and an overview of the HTA program.
3. **Previous meeting business:**

   July 26, 2024 meeting minutes: Draft minutes reviewed. Motion made and seconded to approve the minutes as written.

   Action: Seven committee members approved the July 26, 2024 meeting minutes.
4. **Cochlear implants**

   HTCC reviewed and supplemental materials.

   Action: Seven committee members voted that the evidence presented would not change the previous determination
5. **Treatments for chondral defects of the knee**

   HTCC discussion and action:

   Discussion

The committee discussed and deliberated on key health outcomes by incorporating information from a comprehensive and current evidence report, public comments, and state agency utilization information. The committee discussed and voted separately on the evidence for the use of matrix-induced autologous chondrocyte implantation (MACI), osteochondral autologous transplantation (OATS)/osteochondral allograft transplantation (OCA), and cell-free implants and autologous matrix-induced chondrogenesis (AMIC) for the treatment of chondral defects of the knee. The committee decided that the current evidence on MACI and OATS/OCA is sufficient to determine coverage with conditions. The committee considered the evidence, public comment, and expert input, and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to cover with conditions MACI and OATS/OCA for the treatment of chondral defects of the knee. The committee voted not to cover cell-free implants and AMIC.

	Not covered	Covered with conditions	Covered unconditionally
Matrix-induced autologous chondrocyte implantation (MACI)	0	7	0
Osteochondral autologous transplantation (OATS)/ osteochondral allograft transplantation (OCA)	0	7	0
Cell-free implants and autologous matrix-induce chondrogenesis (AMIC)	7	0	0

Discussion

The committee reviewed and discussed the available studies for MACI, OATS/OCA, cell-free implants, and AMIC for treatments of chondral defects of the knee. Conditions for coverage were discussed, drafted, and voted on. All committee members present supported the conditions of coverage of MACI and OATS/OCA. Details of study design, inclusion criteria, outcomes, cost, cost-effectiveness, and other factors affecting study quality were discussed as well as clinical application.

Decision

Treatments for chondral defects of the knee are covered with conditions for the following:

- MACI (and other FDA-approved 3rd generation ACI) for the treatment of chondral defects of the knee is a covered benefit with conditions:
    - Symptomatic, single or multiple full-thickness (Outerbridge Classification of Grade III or IV) articular cartilage defects of the femoral condyle (medial, lateral, or trochlea) and/or patella at least 3cm² in size;
    - Documented closure of growth plates in adolescent individuals;
    - Age <50, older at the discretion of the agency;
    - Body mass index less than 35; and

    - Excluding malignancy, degenerative (Kellgren-Lawrence Grade 3 or 4) and inflammatory arthritis in the joint,
- OATS/OCA for the treatment of chondral defects of the knee is a covered benefit with conditions:
    - Symptomatic, single or multiple full-thickness (Outerbridge Classification of Grade III or IV) articular cartilage defects of the femoral condyle (medial, lateral, or trochlea) and/or patella;
    - For OATS, articular cartilage lesions that are between 2cm² and 4cm² in size;
    - Documented closure of growth plates in adolescent individuals;
    - Age <50, older at the discretion of the agency;
    - Body mass index less than 35; and
    - Excluding malignancy, degenerative (Kellgren-Lawrence Grade 3 or 4) and inflammatory arthritis in the joint
- Not covered with:
    - Uncorrected malalignment, unless a corrective procedure done prior to, or concomitantly
    - Uncorrected ligamentous deficiency, unless a corrective procedure is done prior to, or concomitantly

Cell-free implants and autologous matrix-induce chondrogenesis (AMIC) are not a covered benefit for treatments of chondral defects of the knee.

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). Based on the information provided in the systematic review, there is no NCD for treatments reviewed for chondral defects of the knee.

The committee discussed clinical guidelines identified from the following organizations:

- Knee Pain and Mobility Impairments: Meniscal and Articular Cartilage Lesions Revision 2018: Clinical Practice Guidelines Linked to the International Classification of Functioning, Disability and Health from the Orthopaedic Section of the American Physical Therapy Association (2018)
- Consensus Guidelines on Interventional Therapies for Knee Pain (STEP Guidelines) from the American Society of Pain and Neuroscience (2022)
- Mosaicplasty for symptomatic articular cartilage defects of the knee: National Institute for Health and Care Excellence (NICE) (2018)

The recommendations of the guidelines vary. The committee's determination is consistent with the noted guidelines.

HTA staff will prepare a findings and decision document on treatments for chondral defects of the knee for public comment to be followed by consideration for final approval at the next committee meeting.

6. Meeting adjourned

Washington State Health Care Authority

Treatments for chondral defects of the knee

Draft findings and decision
Timeline, overview and comments

Timeline

Phase	Date	Public Comment Days
Selected technologies published	July 7, 2023	
Public comments	July 7 to August 7, 2023	**31**
Draft key questions published	December 22, 2023	
Public comments	Dec. 22, 2023 to January 5, 2024	**15**
Final key questions published	January 22, 2024	
Draft report published	June 28, 2024	
Public comments	June 28 to July 29, 2024	**32**
Final report published	August 23, 2024	
Public meeting	September 20, 2024	
Draft findings & decision published	October 2, 2024	
Public comments	October 2 to 16, 2024	**15**

Overview

Category	Comment Period *October 2 to 10, 2024*	Cited Evidence
Patient, relative, and citizen	0	-
Legislator and public official	0	-
Health care professional	2	Yes
Industry & manufacturer	1	Yes
Professional society & advocacy organization	0	-
Total	**3**	

Comments

	Respondents	Representing	Cited Evidence
☐ 1.	Ty Jones, MD	Regence BlueShield WA	Yes
☐ 2.	Carolyn Garziano	Smith & Nephew	Yes
☐ 3.	Ty Jones, MD	Regence BlueShield WA	Yes

From: [redacted]
To: HCA ST Health Tech Assessment Prog
Subject: Public comment on draft findings and decision on treatments for chondral defects of the knee
Date: Wednesday, October 2, 2024 4:38:57 PM
Attachments: mg_info.txt

External Email

I appreciate the committee's thoughtful approach to this complex topic and the well-written draft.

I request a change for clarity with no change to intent to the following two Limitations of Coverage:

- For MACI, applies to articular cartilage lesions ≥3cm^2 in size;
- For OATS, applies to articular cartilage lesions 2cm^2 - 4cm^2 in size;

The request is to remove "applies to" in both instances.

I believe that the intent of these two Limitations of Coverage is to limit MACI coverage to articular cartilage lesions ≥3cm^2 in size and to limit OATS to articular cartilage lesions 2cm^2 - 4cm^2 in size. My concern is that the use of the word "applies" in the LOC may create confusion for health plans administering it, based on what those health plans do when an HTCC does not apply to a particular request. If the HTCC does not apply to the indication for the request, the request is not reviewed against the HTCC and is instead reviewed against the Agency's own medical policy. In this particular instance, by stating that the Limitations of Coverage for MACI applies to articular cartilage lesions ≥3cm^2 in size, a health plan may interpret that the HTCC does not apply to requests for MACI for articular cartilage lesions < 3cm^2 in size and should therefore review these requests against their own medical policy. This may inadvertently result in a medical necessity determination of approved as medically necessary, denied as investigational, or denied as not medically necessary based on interpretation of the Agency's policy, while the HTCC's intent is that the request be denied as not meeting the limitations of coverage. The same would be true for OATS requests for articular lesions <2cm^2 and >4cm^2.

To eliminate this confusion and to be consistent with the way the other Limitations of Coverage are written in this Decision, please consider removing the word "applies to" and simplify to:

- For MACI, articular cartilage lesions ≥3cm^2 in size.
- For OATS, articular cartilage lesions 2cm^2 - 4cm^2 in size.

Ty Jones, MD, CAQSM, CPPS, CPHQ (he/him)
Health Care Authority Medical Director
Cambia Health Solutions
[redacted]

[redacted]

[redacted]

From: [redacted]
To: HCA ST Health Tech Assessment Prog
Subject: Public Comment HTCC Draft Findings & Decision Treatment for Chondral Defects of the Knee (20240920A)
Date: Monday, October 14, 2024 4:54:53 AM
Attachments: image001.png
HCA Comments 10.2024_v2.docx
Agili-C ECRI report.pdf
singlestep-scaffold-insertion-for-repairing-symptomatic-chondral-knee-defects-pdf-1899876581008837.pdf

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External Email

Dear HTCC Committee:

Attached please find the following documents in response to request for comment:

1. Letter of comment
2. ECRI Report – Agili-C Cell-Free Osteochondral Scaffold
3. NICE Interventional Procedure Guidance, Single-Step Scaffold Insertion for Repairing Symptomatic Chondral Knee Defects

Thank you for the opportunity to comment and for considering this additional information in your final decision. Please feel free to reach out if you require any additional clarification.

Best Regards,

SmithNephew
Dr. Carolyn J. Graziano, DPT, MBA, CPC
Director, Strategic Reimbursement | Value Generation | Market Access
Sports Medicine
[redacted]

Smith & Nephew, Inc.
[redacted]
[redacted]

Dear HCA HTA Program Committee:

I am writing to provide public comment to the HTCC Draft Findings and Decision ***Treatment for Chondral Defects of the Knee*** (20240920A). I am requesting reconsideration of the Agili-C Cell-Free Implant for inclusion for coverage. Changing the determination of Cell-Free Implant from "not a covered benefit" to "covered benefit with conditions" is consistent with the evidence analysis of the HTA as reported in the Final Evidence Report, ***Treatment of Chondral Defects of the Knee***, August 21, 2024.

Patient access to new technology is critical to improve health outcomes and deter disease process whenever possible. While the current covered procedures such as MACI, OCA and OATS offer some improvement over the standard of care, there are still gaps in patient access and unmet clinical needs.

S+N strongly supports the evidence analysis of the HTA. Both MACI and OATS currently have the highest volume of studies with MACI demonstrating moderate certainty of evidence. Cell-Free Implant also demonstrates moderate certainty of evidence for PROs and Responder based on review of 1 RCT (n=251). The only studies for OCA were 2 NRSIs comparing OCA to OATS with low certainty of evidence of the need for reoperation. Similar to OCA, AMIC had only one small RCT with low and very low certainty of evidence.

Based on the HTA evidence analysis, the coverage determinations for MACI, OATS and AMIC are consistent with the certainty of evidence. However, the coverage determinations for OCA and Cell-Free Implant do not seem to follow the same standard.

The summary of COE ratings for selected comparisons of chondral defect procedures for the knee included in the HTA does not include Osteochondral Allograft (OCA) as a distinct procedure yet OCA is included in the Draft Findings & Decision as a "covered benefit" as if it is the same as OATS.

Figure ES-2. Summary of COE Ratings for Selected Comparisons of Chondral Defect Procedures of the Knee Included in This HTA

Comparison	*MACI vs. MF*	*OATS vs. MF*	*1st Line vs. 2nd Line[b]*	*Cell-free implant vs. MF/ Chondroplasty*	*AMIC vs. MF*
PROs	*Favors MACI*	*Comparable*		*Favors cell-free implant*	*Favors AMIC*
	Favors MACI	*Comparable*	*Favors 1st line*		
Responder	*Favors MACI*	*Favors OATS*		*Favors cell-free implant*	
	Favors MACI				
Treatment Failure	*Comparable*	*Favors OATS*		*Comparable*	
	Comparable	*Favors OATS*	*Favors 1st line*		
Re-operation	*Comparable*	*Comparable*			*Comparable*
	Favors MACI		*Favors 1st line*		
Harms[a]	*Comparable*	*Comparable*		*Favors cell-free implant[c]*	*Unable to determine direction of effect*
	Comparable				

RCT COE (Solid): High COE | Moderate COE | Low COE | Very Low COE

NRSI COE (Pattern): High COE | Moderate COE | Low COE | Very Low COE

As I am sure the committee is aware, OATS (osteochondral autologous transfer) and OCA (osteochondral allograft) are two distinct procedures described by two separate CPT Codes (27416 and 27415) with different payment rates and unique evidence. The studies supporting OATS are not applicable to OCA.

Again, I am requesting reconsideration of Agili-C Cell-Free Implant as a covered benefit. OCA meets the committee's standard for coverage based on 2 NRSI with low certainty of evidence for PROs, treatment failure and responder. Cell-Free Implant demonstrates (statistically significant improvement) across all five outcomes (PROs, Responder, Treatment Failure, Re-operation[1], and Harms) and moderate certainty of evidence for PROs and Responder and therefore, should also meet the standard for coverage.

Agili-C Cell-Free implant is certainly not in the same category as AMIC based on study sample size and certainty of evidence and should not be included as a "not covered benefit." At the very least, consideration for coverage of Agili-C Cell Free-Implant should be available to HCA beneficiaries on a medically necessary review basis.

One limitation noted about the Cell-Free Implant evidence was lack of long-term clinical data. Subsequent to the HTA review, 4-year data (n=247) was published. At 48-month follow-up, 1.2% (n = 2) of patients in the scaffold group (cell-free) and 9.5% (n = 8) of patients in the control group had undergone a knee replacement or osteotomy (p = 0.003) demonstrating statistically significant improvement for re-operation rates for the Agili-C Cell-Free Implant group. And as with previous time points regardless of lesion location (trochlear or condyle), patients who received the Agili-C Cell-Free implant maintained statistically significantly higher KOOS overall scores compared to surgical standard of care.[1]

Other considerations in support of including Agili-C Cell Free Implant as a covered benefit include:

- ECRI Clinical Evidence Assessment (attached) for Agili-C Cell-free Osteochondral Scaffold from June of 2022 has a favorable evidence bar rating of 4/5. The assessment notes "evidence from one randomized control trial (RCT) and four pre-post studies indicates Agili-C improves knee function and activities of daily living. The RCT also indicates that Agili-C improves patient-oriented outcomes more than surgical treatment (e.g., debridement, microfracture)."

- NICE Interventional Procedure Guidance (attached) published September 3, 2024, Single-step scaffold insertion for repairing symptomatic chondral knee defects. This guidance recommends using single-step scaffold insertion as an option for repairing symptomatic chondral knee defects with standard arrangements in place for clinical governance, consent, and audit.

Thank you for the opportunity to comment and for your reconsideration for coverage for Agili-C Cell Free Implant. We would welcome the opportunity to meet with you to discuss the evidence and serve as a resource as the Health Technology Clinical Committee develops its final findings.

Sincerely,

Dr. Carolyn J Graziano, DPT, MBA, CPC
Director, Strategic Reimbursement |Value Generation| Market Access

[1] Conte P, Anzillotti G, Crawford DC, et al. Differential analysis of the impact of lesions' location on clinical and radiological outcomes after the implantation of a novel aragonite-based scaffold to treat knee cartilage defects. *Int Orthop*. Published online September 21, 2024. doi:10.1007/s00264-024-06314-1

ECRI

CLINICAL EVIDENCE ASSESSMENT

Agili-C Cell-free Osteochondral Scaffold (Smith & Nephew, Inc.) for Knee Cartilage Repair

Description: Agili-C is an implant made of inorganic calcium carbonate (aragonite) intended to repair chondral and osteochondral defects in the joint. The cell-free, biodegradable implant has a resorbable biphasic scaffold and surface micro-drilled layer treated with hyaluronic acid.

Intended benefit: Agili-C is intended to repair chondral and osteochondral defects in joints by stimulating cartilage growth. Agili-C is intended as an alternative to standard surgical treatments (e.g., debridement, microfracture), autografts, biologic and cell-based regenerative treatments, and use of other natural, tissue-engineered, or inorganic grafts.

Focus: This report focuses on Agili-C's safety and effectiveness for treating cartilage and osteochondral defects in the knee compared with those of other knee cartilage repair approaches.

The Evidence Bar™ - Favorable

Conclusions: Evidence from one randomized control trial (RCT) and four pre-post studies indicates Agili-C improves knee function and activities of daily living. The RCT also indicates that Agili-C improves patient-oriented outcomes more than surgical treatment (e.g., debridement, microfracture).

Rationale: Consistent findings from one RCT and four small pre-post studies enable low-confidence conclusions. Included studies had a narrow patient demographic population (e.g., young, majority male), which limits the conclusion's generalizability. Patient-oriented outcomes were self-reported in nonblinded studies, increasing the risk for bias. No studies reported on comparator implants or plugs and other types of surgical standard of care. No studies reported on patient-oriented outcomes beyond five years.

Evidence gaps: Additional RCTs that assess patient-oriented outcomes in a diverse patient population, with longer follow-up times (i.e., >5 years), and compare Agili-C with surgical knee cartilage repair approaches are needed to support higher-confidence conclusions. Studies comparing Agili-C with other grafts are also needed. One ongoing RCT will not address these gaps.

Product Description

Agili-C (CartiHeal, Inc., HaMerkaz, Israel, a subsidiary of Smith & Nephew, Inc., Andover, MA, USA) is a scaffold intended to treat cartilage and osteochondral lesions on the knee-joint surface caused by trauma or osteoarthritis, which can greatly affect quality of life (QOL) due to pain and limited mobility. Cartilaginous tissue is avascular, contributing to poor healing. If left untreated, lesions caused by trauma can deteriorate to secondary osteoarthritis. Standard of care treatments include use of knee braces, medication, and activity limitation. Surgical treatments include debridement, articular cartilage stimulation, osteochondral autograph transfers, chondrocyte implantation, other implants, and joint replacement. (See the OrthroInfo.com article Articular Cartilage Restoration.)

Agili-C is a biocompatible and biodegradable implant made of aragonite (calcium carbonate) derived from coral exoskeleton. The top surface micro-drilled layer is treated with hyaluronic acid to help regenerate a cartilaginous matrix. The porous aragonite scaffold is intended to promote osteoclast and osteoblast adhesion for bone remodeling and cartilage regeneration. Agili-C is 10 mm in length and is available in four diameters (7.5, 10, 12.5, and 15 mm). An orthopedic surgeon implants Agili-C into the lesion defect in an operating room, with the patient under general anesthesia. The surgeon first assesses the lesion by arthroscopic surgery. Next, the surgeon performs a mini-arthrotomy, measures the lesion dimensions, and prepares the site for implant insertion using the accompanying surgical toolset. The surgeon manually "press-fits" the implant into the lesion site. Patients are discharged the day after surgery with a knee brace and undergo standardized postoperative rehabilitation. (See the manufacturer's website.)

Regulatory Status

Premarket Approval (PMA)

FDA granted PMA to the Agili-C Osteochondral Scaffold on March 29, 2022 (P210034). The labeled indication reads: "The Agili-C scaffold is indicated for the treatment of an International Cartilage Repair Society (ICRS) grade III or above knee-joint surface lesion(s), with a total treatable area of 1-7cm2, without severe osteoarthritis (Kallgren-Lawrence Grade 0-3)."

Clinical Literature

Search dates: all available literature published through May 2, 2022. We reviewed full text of 5 studies reporting on 384 patients.

We searched PubMed, EMBASE, and selected web-based resources for documents relevant to this topic. Our search strategies included the following keywords: agili-c, aragonite, cartiheal. Please see the *Selected Resources and References* section for detailed search strategies.

Study selection criteria: We included studies that reported on patient-oriented clinical outcomes (e.g., pain, physical function, QOL, adverse events [AEs]) in patients who underwent knee cartilage repair with Agili-C implants. We excluded from review radiographic and histopathologic outcomes that do not necessarily correlate well with patient-oriented outcomes. We excluded from review studies with fewer than 10 patients per arm and conference presentation abstracts. We identified and reviewed one study described in Agili-C's FDA Summary of Safety and Effectiveness Data (SSED) document and full-text publications of four other studies.

Included studies:

- 1 RCT that provided data for Agili-C's PMA application compared Agili-C (n = 167) with standard surgical care (n = 84) in patients with cartilage or osteochondral lesions of the knee and reported on Knee Injury and Osteoarthritis Outcome Score (KOOS) scores, International Knee Documentation Committee (IKDC), Tegner activity, and AEs at 2-year follow-up.
- 1 prospective pre-post study (Van Genechten et al. 2021, n = 13) reported on KOOS subscores, IKDC score, Lysholm score, Tegner activity, and AEs at 3-year follow-up in patients with knee joint surface lesions.(1)
- 1 prospective pre-post study (Kon et al. 2021, n = 86) reported on KOOS subscores and IKDC scores at 2-year follow-up.(2)

- 1 prospective pre-post study (Kon et al. 2016, n = 21) reported on KOOS, IKDC, Lysholm scores, and AEs at 1-year follow-up for patients who received Agili-C implants.(3) Authors compared outcomes with those in historical controls who received an early cylindrical Agili-C version. We excluded these data from review because the cylindrical implant version is no longer commercially available.
- 1 retrospective study (Andor et al. 2021, n = 13) reported on KOOS, IKDC scores, and AEs for patients who received Agili-C implants at 1-year follow-up.(4) The study also reported on patients treated with Hyalograft-C (n = 3) and Chrondotissue (n = 7) implants. We excluded outcomes for those patients from review because each group included fewer than 10 patients and because authors made no between-group comparisons.

See Table 1 for study summaries. We review full text of the included studies available through open access or our library subscriptions and abstracts of other studies.

Excluded studies: We excluded from review a study that reported pooled data from patients treated with Agili-C and other grafts.(5)

Findings

We assessed one RCT and four pre-post studies.

- *KOOS:* KOOS is a 42-item validated questionnaire with 5 subscales. Patients self-report knee-specific outcome measures. The total score and subscores are transformed into a scale that ranges from 0 (severe problems) to 100 (no problems).
  - *Overall:* An RCT that served as Agili-C's U.S. pivotal trial and is described in Agili-C's FDA SSED reported increased mean differences from baseline to 2 years in overall improvement for Agili-C (42.65, 95% confidence interval [CI] 39.55 to 45.54) compared with surgical standard of care (SSOC) (21.39, 95% CI 17.35 to 25.71).
  - *Pain*: The pivotal RCT reported decreased pain in the Agili-C group (41.52, 95% CI 38.51 to 44.09) compared with SSOC (21.20, 95% CI 17.26 to 25.11) at 2 years. Kon et al. 2021 reported improved pain outcomes after 2 years (79.5 ±21.1) compared with 6-month follow-up (79.5 ±21.1, p <0.001).(2) Andor et al. 2016 reported improvement at 1 year (66.1) compared with baseline (54.8, p <0.05).(4) Kon et al. 2016 reported improved symptoms at 1 year (81.4 ±13.9) compared with baseline (52.0 ±14.8, p <0.005).(3) Van Genechten et al. 2021 reported that pain improved (41.2 ± 14.7) at 3-year follow-up compared with baseline.(1)
  - *ADL:* The pivotal RCT reported higher ADL scores for Agili-C (37.59, 95% CI 34.94 to 40.29) than for SSOC (18.35, 95% CI 14.62 to 22.12) at 2 years. Kon et al. 2021 reported improved ADL scores at 2 years (84.1 ±21.4) compared with baseline (56.1 ±18.4, p <0.001).(2) Andor et al. 2016 reported improved scores at 1 year (76.3) compared with baseline (64.2, p <0.05).(4) Kon et al. 2016 reported improved scores at 1 year (86.6 ±13.5) compared with baseline (56.4 ±18.0, p <0.005).(3) The pivotal RCT reported superiority and higher Sports scores for Agili-C (53.65, 95% CI 49.51 to 57.64) than for SSOC (25.81, 95% CI 20.16 to 31.60) at 2 years. Kon et al. 2021 reported improved Sport scores at 2 years (60.8 ±31.9) compared with 6-month follow-up. (48.1 ±29.5, p <0.001).(2) Andor et al. 2016 reported improvement at 1 year (60.8) compared with baseline (38.3, p <0.05).(4) Kon et al. 2016 reported improved scores at 1 year (59.5 ±30.2) compared with baseline (29.1 ± 24.3, p <0.005).(3)
  - *QOL:* The pivotal RCT reported higher QOL scores for Agili-C (47.29, 95% CI 43.50 to 52.24) than for SSOC (23.49, 95% CI 18.05 to 28.80) at 2 years. Kon et al. 2021 reported improved QOL scores at 2 years (54.9 ±30.4) compared with 6-month follow-up (44.7 ±27.6, p <0.001).(2) Andor et al. 2016 reported improvement at 1 year (60.7) compared with baseline (40.1, p <0.05).(4) Kon et al. 2016 reported improved scores at 1 year (50.6 ± 27.7) compared with baseline (22.0 ±16.7, p <0.005).(3)
  - *Symptoms:* The pivotal RCT reported superiority and higher scores for Agili-C (33.30, 95% CI 30.59 to 36.15) than for SSOC (18.151, 95% CI 14.21 to 22.06) at 2 years. Kon et al. 2021 reported improved Symptom scores at 2 years (77.7 ±21.2) compared with baseline (55.4 ±19.9, p <0.001).(2) Andor et al. 2016 reported improvement at 1 year (71.9) compared with baseline (58.2, p <0.05).(4) Kon et al. 2016 reported improved scores at 1 year (79.8 ±17.6) compared with baseline (55.6 ±23.4, p <0.005).(3)
- *IKDC:* IKDC is a patient-reported outcome measure on overall knee function score with three subscales (e.g., symptoms, sports activity, knee function). The total score is summed from individual items, transformed, and

scaled from 0 (lowest level of function or highest level of symptoms) to 100 (highest level of function and lowest level of symptoms). Van Genechten et al. reported increased IKDC scores postoperatively (75.9 ±20.9) compared with baseline (41.9 ±13.8, p = 0.0002) at 3-year follow-up.(1) Kon et al. 2021 reported improved scores at 2 years (65.8 ±23.5) compared with baseline (37.8 ±14.7, p <0.001).(2) The pivotal RCT reported clinically important differences between Agili-C and SSOC at 2 years (22.7, 95% CI 22.7 to 28.6). Kon et al. 2016 reported improved scores at 1 year (63.2 ±18.0) compared with baseline (36.5 ±14.2, p <0.005).(3)

- *Lysholm knee scoring scale:* The Lysholm scale is a patient-reported outcome measure on symptoms that affect ADLs. The total score can range from 0 to 100, with the following assignments: <65 is "poor," 65 to 85 is "fair', 84 to 94 is "good," 95 to 100 is "excellent." Van Genechten et al. 2021 reported increased Lysholm scores postoperatively at 3-year follow-up (85.4 ±15.4) compared with baseline (41.9 ±13.8, p = 0.0017).(1) Kon et al. 2016 reported improved scores at 1 year (75.6 ±17.2) compared with baseline (54.8 ±18.5, p <0.005).(3)
- *Tegner scores:* The Tegner score is a self-reported outcome to determine patient activity level before and after a knee injury. It is reported on a scale of 0 (disabled) to 10 (professional athlete). Van Genechten et al. 2021 report score improvement from baseline (2.7 ±1.8) to 18 months (4.7 ±1.6, p = 0.0418) and 2 years (4.9 ±1.4, p = 0.0104), but improvement was not reported at 3 years (4.6 ±2.2, p = 0.0698).(1) The pivotal RCT reported a mean score improvement from baseline to 2 years for Agili-C (2.5, 95% CI 0.0 to 8.0) compared with SSOC (1.0, 95% CI -2.0 to 8.0).
- *AEs*: Van Genechten et al. 2021 reported five possible device-related AEs, including four moderate and one severe AE.(1) Kon et al. 2021 reported 36 AEs, including 8 (9.3%) implant removals by 2-year follow-up.(2) Andor et al. 2016 did not report any AEs.(4) The pivotal study reported fewer prespecified AEs for Agili-C (23.4%) than with SSOC (50%) at two years. Fewer treatment failures occurred in the Agili-C group (7.2%, n = 12) than in the SSOC group (21.4%, n = 18, p = 0.002).

Evidence limitations: Consistent evidence across all included studies indicates Agili-C improves patient-oriented outcomes when used to treat knee joint surface lesions. However, evidence gaps remain. Only one study compared Agili-C with SSOC, and one other study compared Agili-C with other implants. No studies reported longer-term outcomes (i.e., >5 years), which is needed to determine the treatment's long-term safety and efficacy. All studies had small sample sizes and focused on a narrow demographic patient population. The studies were not blinded; therefore, self-reported patient-oriented outcomes in the RCT comparing Agili-C and SSOC are at risk of bias. Larger RCTs that include wider and more balanced patient demographic (i.e., age, gender, activity level) that compare Agili-C with SSOC and competing implants would help support stronger and more generalizable conclusions.

Table 1. Product-specific Clinical Literature

Author/ Year	Study Type and Patients	Treatment(s)	Findings Reported by Authors	Authors' Conclusions
Van Genechten et al. 2021(1) Reviewed full text Belgium NCT02423629 3-year follow-up Manufacturer-sponsored study	Prospective, single-site, pre-post study (n = 13) of patients with knee joint surface lesions (JSLs)	Agili-C	"Primary outcome (KOOS [Knee Injury and Osteoarthritis Outcome Score] pain) improved with 36.5 ± 14.7 points at 12 months (P = 0.002) and 41.2 ± 14.7 points at 36 months (P = 0.002) follow-up. Similar increasing trends were observed for the other KOOS subscales, IKDC [International Knee Documentation Committee], and Lysholm score, which were significantly better at each follow-up time point relative to baseline (P < 0.05). Activity level increased from 2.75 ± 1.6 to 4.6 ± 2.2 points at final follow-up (P = 0.07) [at 36 months]….No serious adverse events were reported." Tabulated data: IKDC: baseline 41.9 ±13.8, 36 months 75.9 ±20.9, p = 0.0002; Lysholm score: baseline 52.1 ±17.9, 36 months 85.4 ±15.4, p = 0.0017; Tegner score: baseline 2.7 ±1.8, 18 months 4.7 ±1.6, p = 0.0418, 24 months 4.9 ±1.4, p = 0.0104.	"The study demonstrated that the biphasic aragonite-based scaffold is a safe and clinically effective implant for treating small-medium sized JSLs of the distal femur in a young and active patient cohort. the implant showed satisfying osteointegration and restoration of the osteochondral unit up to 3 years postimplantation."
Kon et al. 2021(2) Reviewed full text (available only by subscription) Europe	Prospective, multicenter, pre-post study (n = 86) of adult patients with JSL in knee osteoarthritis (OA)	Agili-C	"Significant improvement on all KOOS subscales was recorded from baseline (Pain: 49.6 ±13.1; Activities of Daily Living [ADL]: 56.1 ±18.4; Sport: 22.8 ±18.8; Quality of Life [QoL]: 23.5 ±16.5; Symptoms: 55.4 ±19.9) to the 24 months' follow-up (Pain: 79.5 ±21.1 [P < .001]; ADL: 84.1 6 21.4 [P < .001]; Sport: 60.8 ±31.9 [P < .001]; QoL: 54.9 ±30.4 [P < .001]; Symptoms: 77.7 ±21.2 [P < .001]). The IKDC subjective score showed a similar trend and improved from 37.8 ±14.7 at baseline to 65.8 ±23.5 at 24 months (P < .001)…Treatment failure requiring revision surgery occurred in 8 patients (9.3%)."	"The use of an aragonite-based osteochondral scaffold in patients with JSLs and mild to moderate knee OA provided significant clinical improvement at the 24-month follow-up, as reported by the patients. These findings were associated with good cartilage defect filling, as observed on MRI [magnetic resonance imaging]."
CartiHeal, Inc. 2021 Reviewed FDA Summary of Safety and	Open-label, multicenter, RCT (n = 251) of adults with a diagnosis of cartilage or	Agili-C (n = 167) or surgical standard of care (SSOC) (n = 84)	"The overall adverse event ('AE') rate was lower for the Agili-C™ group (58.7%) compared to the SSOC group (77.4%)." "IKDC change from baseline in the Agili-C™ group was…43.0±21.2 at	"The data in this application support the reasonable assurance of safety and effectiveness of this device when

Author/ Year	Study Type and Patients	Treatment(s)	Findings Reported by Authors	Authors' Conclusions
Effectiveness Data document United States, Belgium, Hungary, Israel, Italy, Poland, Romania, Serbia Manufacturer Sponsored-study	osteochondral knee lesions		24 months. These results show that the IKDC scores are substantially higher than a minimal clinically important difference (MCID) of 16.7." Tabulated KOOS scale mean differences from baseline to 24 months: overall score, Agili-C 42.65 (95% CI 39.55 to 45.54) and SSOC 21.39 (95% CI: 17.35 to 25.71); pain, Agili-C 41.52 (95% CI: 38.51 to 44.09) and SSOC 21.20 (95% CI: 17.26 to 25.11); QOL, Agili-C 47.29 (95% CI: 43.50 to 52.24) and SSOC 23.49 (95% CI: 18.05 to 28.80); ADL, Agili-C 37.59 (95% CI: 34.94 to 40.29) and SSOC 18.35 (95% CI: 14.62 to 22.12), Sports, Agili-C 53.65 (95% CI: 49.51 to 57.64) and SSOC 25.81 (95% CI: 20.16 to 31.60); Symptoms, Agili-C 33.30 (95% CI: 30.59 to 36.15;) and SSOC 18.15, (95% CI 14.21 to 22.06). Tegner mean score change from baseline to 24 months: Agili-C: 2.5 (95% CI: 0.0 to 8.0) and SSOC 1.0 (95% CI: -2.0 to 8.0).	used in accordance with the indications for use."
Andor et al. 2016 (4) Reviewed full text Romania	Single-site, retrospective study of patients (n = 23) with knee articular cartilage defects	Agili-C (n = 13), Hyalograft-C (n = 3), or Chondrotissue (n = 7); no implant comparisons were made.	"The follow-up assessments demonstrated clinically and statistically significant improvements ($p < 0.05$) in all clinical outcome scores, as compared to the respective preoperative values: IKDC (48.9/77.1 for Chondrotissue implants), KOOS symptoms (58.2/71.9 for Agili-C implants), KOOS pain (54.8/66.1 for Agili-C implants), KOOS daily living activities (64.2/76.3 for Agili-C implants), KOOS sports (38.3/60.8 for Agili-C implants), KOOS quality of life (40.1/60.7 for Agili-C implants) demonstrating improvements in the case of implants previously mentioned."	"Our observations suggest that patients with Agili-C and Hyalograft-C present the best enhancements of IKDC and KOOS scores during a 12-month clinical follow-up."

Author/ Year	Study Type and Patients	Treatment(s)	Findings Reported by Authors	Authors' Conclusions
Kon et al. 2016(3) Reviewed full text (available only by subscription)	Prospective, single-site pre-post study of patients (n = 21) with focal chondral-osteochondral knee lesions	Agili-C implant (n = 21)	"A statistically significant improvement in all clinical scores was documented. In particular, in the tapered implant group the IKDC subjective score increased from 36.5 ± 14.2 to 58.9 ± 18.5 at 6 months and 63.2 ± 18.0 at 12 months (P < 0.005). Similarly, the Lysholm score increased from 54.8 ± 18.5 to 70.9 ± 16.5 at 6 months and 75.6 ± 17.2 at to 12 months (P < 0.005). An increase was also recorded in all KOOS subscales." Tabulated KOOS subscores at baseline and 12-month follow-up (p <0.005 for all comparisons): symptoms, 55.6 ±23.4 to 79.8 ±17.6; pain, 52.0 ±14.8 to 81.4 ±13.9; ADL, 56.4 ±18.0 to 86.6 ±13.5; Sport, 29.1 ±24.3 to 59.5 ± 30.2; QoL, 22.0 ±16.7 to 50.6 ±27.7	"This aragonite-based implant was associated with a significant clinical improvement at the 12-month follow-up. Moreover, MRI findings revealed graft integration with good bone and cartilage formation."

Safety

No ECRI Healthcare Product Alerts or MAUDE reports identified.

We searched ECRI's proprietary Healthcare Product Alerts database for product-specific alerts and recalls, and FDA's Manufacturer and User Facility Device Experience (MAUDE) database for AE reports filed during the last 12 months.

Ongoing Trials

One ongoing trial will not address evidence gaps.

Our search of ClinicalTrials.gov for relevant ongoing trials identified only the U.S. pivotal trial, which is expected to report outcomes at up to two-year follow-up. See Table 3 for study details.

Table 2. Ongoing Trial Identified in ClinicalTrials.gov

Study Name/ Identifier from Clinical Trials.gov	Planned Enrollment (n per group)	Study Design Stated Objectives Primary Endpoints to Be Reported	Estimated Date of Completion
Agili-C™ Implant Performance Evaluation NCT03299959	251	"Prospective, multicenter, open-label, randomized, and controlled trial of Agili-C™ vs. SSOC [surgical standard of care] for the repair of joint surface lesions." Primary endpoint: Change in Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee (IKDC) Knee Examination Form 2000, IKDC Subjective Knee Evaluation, SF-12 Health Survey, and Tegner Activity Score at up to 2-year follow-up.	January 2023

Selected Resources

ECRI. Available from: www.ecri.org. Subscription required.

- Agili-C. FDA Approvals & Clearances. 2022 Apr.
- Autologous chondrocyte implantation for repairing osteochondral knee defects. Clinical Evidence Assessment. 2020 Jun.
- CartiMax Viable Cartilage Allograft (MTF Biologics) for repairing knee cartilage. Clinical Evidence Assessment. 2019 Apr.
- Combined autologous chondrocyte implantation and osteochondral autograft for repairing osteochondral knee defects. Clinical Evidence Assessment. 2019 Nov.
- MACI Autologous Chondrocyte Implant (Vericel Corp.) for repairing knee cartilage defects in adults. Clinical Evidence Assessment. [updated 2018 Nov].
- Osteochondral autologous and allogeneic grafts for repairing knee cartilage. Clinical Evidence Assessment. [updated 2020 Jul].

PubMed. National Library of Medicine. Available from: www.pubmed.gov.

- #1 "agili c*" OR agilic*
- #2 cartiheal[tiab] OR "carti heal"[tiab] OR (bioventus[tiab] AND implant* AND (knee OR knees))
- #3 aragonite AND implant* AND (knee OR knees)
- #4 NCT01471236 OR NCT02423629 OR NCT02831244 OR NCT03299959
- #5 #1 OR #2 OR #3 OR #4

Embase. Elsevier B.V. Available from: www.embase.com. Subscription required.

- #1 'agili c*' OR agilic*
- #2 cartiheal OR 'carti heal' OR (bioventus AND implant* AND (knee OR knees))
- #3 aragonite AND implant* AND (knee OR knees)
- #4 nct01471236 OR nct02423629 OR nct02831244 OR nct03299959
- #5 #1 OR #2 OR #3 OR #4

FDA website. U.S. Department of Health and Human Services. Available from: www.fda.gov.

We identified one Premarket Approval for Agili-C, listed below.

- Center for Devices and Radiological Health (CDRH) Premarket Approval (PMA). Agili-C. CartiHeal, Ltd. decision date 2022 Apr 30.
- Agili-C – P210034. Recently-Approved Devices. [content current as of 2022 Apr 29].

Manufacturer Website (CartiHeal, Inc., HaMerkaz, Israel, a subsidiary of Smith & Nephew, Inc., Andover, MA, USA)

- Agili-C. [cited 2022 May 2].
  - Publications. [cited 2022 May 2].
  - FDA approves CartiHeal's implant for the treatment of cartilage and osteochondral defects. Press Release. 2022 Mar 30.
- Bioventus exercises call option to acquire CartiHeal. Press Release. 2022 Apr 4.

Additional Resources

- Oliveira JM, Ribeiro VP, Reis RL. Advances on gradient scaffolds for osteochondral tissue engineering. *Progress in Biomedical Engineering*. 2021;3(3):033001.
- Young, R. Landmark cartilage repair study: Agili-C superior over std of care. *Orthopedics This Week*. 2021 Aug 5.

References Reviewed (PubMed and EMBASE search dates: all literature through 2022 May 2)

1. Van Genechten, W, Vuylsteke, K, Struijk, C, Swinnen, L, and Verdonk, P. Joint Surface Lesions in the Knee Treated with an Acellular Aragonite-Based Scaffold: A 3-Year Follow-Up Case Series. *Cartilage*. 2021;13(1_suppl):1217s-1227s. PubMed abstract
2. Kon, E, Di Matteo, B, Verdonk, P, Drobnic, M, Dulic, O, Gavrilovic, G, Patrascu, JM, Zaslav, K, et al. Aragonite-Based Scaffold for the Treatment of Joint Surface Lesions in Mild to Moderate Osteoarthritic Knees: Results of a 2-Year Multicenter Prospective Study. *Am J Sports Med*. 2021;49(3):588-598. PubMed abstract
3. Kon, E, Robinson, D, Verdonk, P, Drobnic, M, Patrascu, JM, Dulic, O, Gavrilovic, G, and Filardo, G. A novel aragonite-based scaffold for osteochondral regeneration: early experience on human implants and technical developments. *Injury*. 2016;47 Suppl 6:S27-s32. PubMed abstract
4. ANDOR, B, PATRASCU, J, Cojocaru, SFD, Sandesc, M, Borcan, F, Boruga, O, and Bolintineanu, S. Comparison of Different Knee Implants Used on Patients with Osteoarthritis Control Study. *Mater Plast*. 2016;53(1):119-125. Full text
5. Boffa, A, Solaro, L, Poggi, A, Andriolo, L, Reale, D, and Di Martino, A. Multi-layer cell-free scaffolds for osteochondral defects of the knee: a systematic review and meta-analysis of clinical evidence. *J Exp Orthop*. 2021;8(1):56. PubMed abstract | Full text

The Evidence Bar™

Definition: A visualization of our judgment about the balance of benefits and harms of the technology after assessing the available published clinical evidence in light of key outcomes and comparisons of interest.

	Unfavorable
	Raises concerns
	Potential disadvantages but too few data Potential disadvantages but very-low-quality data
	Too few data Very-low-quality data Mixed results No data available
	Potential benefits but too few data Potential benefits but very-low-quality data
	Favorable
	Very favorable

Policy Statement

This report addresses a specific inquiry from an ECRI member about a particular brand-name healthcare product and its safety and efficacy. The information contained in this report is highly perishable and reflects the available information we identified at the time this report was prepared. The comments and opinions expressed were accurate to the best of our knowledge at the time of preparation, but are subject to change if and when new information is published. The report summarizes the identified clinical literature (i.e., human studies) and other information that we deemed relevant to the topic within the search dates noted in the clinical literature description. ECRI reviewed the clinical studies in one or more of the following forms: full published articles, article abstracts, FDA Summaries of Safety and Effectiveness Data, and/or conference abstracts or posters. Conference abstracts and posters of clinical studies typically do not provide complete information by which to assess study design or validity of the final published results of a study. Therefore, results presented in these sources of information must be considered with caution. Any and all product claims described in this report were made by the manufacturer in materials it has presented or published about its products. ECRI's description of these claims in this report does not imply any endorsement or agreement. This report is not intended to provide specific guidance for the care of individual patients. ECRI makes no express warranties or any implied warranties regarding the products discussed in this report, including any implied warranty of merchantability or fitness for a particular use. ECRI assumes no liability or responsibility for how members use the information, comments, or opinions contained in Clinical Evidence Assessments.

NICE guidance

Single-step scaffold insertion for repairing symptomatic chondral knee defects

Interventional procedures guidance
Published: 3 September 2024

www.nice.org.uk/guidance/ipg793

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful

discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

This guidance replaces IPG560.

1 Recommendations

1.1 Use single-step scaffold insertion as an option for repairing symptomatic chondral knee defects with standard arrangements in place for clinical governance, consent and audit.

1.2 Healthcare professionals should enter details about everyone having single-step scaffold insertion for repairing symptomatic chondral knee defects onto a suitable registry, such as the International Cartilage Regeneration & Joint Preservation Society Registry.

Why the committee made these recommendations

There is good clinical evidence for the efficacy and safety of this procedure. The evidence shows that it reduces symptoms, stimulates cartilage regeneration, and is safe in the short and medium term. It is an established procedure and more long-term data is being collected. So, it can be used with standard arrangements.

2 The condition, current treatments and procedure

The condition

2.1 Chondral cartilage is the material that covers the end of the bones in the knee joint, to protect them from friction when moving. Damage to this cartilage (chondral knee defect) can cause symptoms such as knee pain and stiffness, and reduced mobility. Untreated full-thickness cartilage lesions may be associated with significant pain and, eventually, arthritis. This is a major cause of disability.

Current treatments

2.2 There are several approaches to managing chondral knee defects. Surgical options depend on the characteristics of the person and the defect. There are 2 main categories of procedure:

- Procedures that mainly aim for symptom relief include:
  - debridement
  - osteotomy
  - knee replacement.
- Procedures that aim for symptom relief and also to re-establish the cartilage surface include:
  - marrow stimulation techniques (such as Pridie drilling and microfracture)
  - mosaicplasty
  - osteochondral allograft transplantation
  - focal articular resurfacing implants
  - autologous chondrocyte implantation (in which chondrocytes harvested

from the knee are cultured and implanted into the damaged cartilage).

Sometimes matrix-induced autologous chondrocyte implantation is done. This is a 2-step procedure because cells have to be cultured outside the body. The cells are harvested for culturing in the first operation, then the cultured cells and scaffold are introduced in the second.

The procedure

2.3 In this procedure, a scaffold is inserted into the area of damaged cartilage to encourage cells to grow into new cartilage. This is a single-step procedure because the cells are not cultured outside the body. A range of techniques can be used to introduce the cells that grow into new cartilage, supported by the scaffold. For example, tiny holes can be drilled into the bone (microfracture) to release the cells, or substances like bone marrow aspirate can be put into the area of damage. Whichever method is used, it is always done in the same operation as the scaffold insertion.

2.4 There are different types of scaffold and ways of doing the procedure. For example, some scaffolds are solid and some are injectable gels. Some of the solid scaffolds must be cut to size and applied over the defect. Other scaffolds are a standard size and shape, and are implanted into the subchondral bone in the damaged area.

2.5 The procedure aims to repair the damaged cartilage, reduce symptoms and keep the joint working.

3 Committee considerations

The evidence

3.1 NICE did a rapid review of the published literature on the efficacy and safety of this procedure. This comprised a comprehensive literature search and detailed

review of the evidence from 12 sources, which was discussed by the committee. The evidence included 5 systematic reviews and meta-analyses, a systematic review and network meta-analysis, 4 randomised controlled trials, a 5-year follow-up analysis of a randomised controlled trial and a registry study. It is presented in the summary of key evidence section in the interventional procedures overview. Other relevant literature is in the appendix of the overview.

3.2 The professional experts and the committee considered the key efficacy outcomes to be: improved quality of life and mobility, and reduced pain.

3.3 The professional experts and the committee considered the key safety outcomes to be: pain, bleeding, infection and failure to improve symptoms.

3.4 Patient commentary was sought but none was received.

Committee comments

3.5 The committee was informed that:

- This procedure can be done by a trained orthopaedic knee surgeon in a general hospital, but more complex defects may need to be referred to a regional specialist centre.
- Like other procedures for chondral knee defects, after the surgery, a rehabilitation programme needs to be followed.
- Different technologies can be used to do this procedure, and they have different amounts of evidence.

3.6 The committee noted that:

- A variety of scaffolds can be used in this procedure. Some, but not all, contain animal products.
- Techniques for introducing the cells that grow into new cartilage are evolving.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

From: [redacted]
To: HCA ST Health Tech Assessment Prog
Subject: Treatment for chondral defects of the knee public comment
Date: Thursday, October 17, 2024 12:10:59 AM

External Email

Hi!

I am submitting a request for an additional qualification to the limitations of coverage, to indicate that the lesion(s) become corrected as unipolar.

The Final Evidence report documents that the local health plans include criteria to assure that the lesion is unipolar (ie that the lesion is not bipolar, described sometimes as having a "kissing lesion" on the opposing articular surface), and I suggest that the HTCC determination include this criteria as well in the limitations of coverage to reflect standards of care and limit member exposure to procedural failures.

Here are some excerpts from several Washington health plan medical necessity criteria for cartilage restoration procedures:

Kaiser: "Defect(s) are **unipolar** – there is **no corresponding kissing lesion** on facing cartilage"

https://wa-provider.kaiserpermanente.org/static/pdf/hosting/clinical/criteria/pdf/knee-arthroscopy-procedures.pdf

Regence: "Focal, full-thickness (grade III or IV) **unipolar** lesions of the patella or on the weight-bearing surface of the femoral condyles or trochlea at least 1.5 centimeters squared in size; and"
https://blue.regence.com/trgmedpol/surgery/sur87.pdf

Cigna: "For femoral and patellar chondral lesions, **absence of a corresponding 'kissing lesion'** with a Modified Outerbridge Classification of Grade III or IV of the distal femur (trochlea, condyles), patella, or tibia"

https://www.evicore.com/sites/default/files/clinical-guidelines/2023-08/Cigna_CMM-312_Knee_Surgery_Arthroscopic_and_Open_V102023_eff05312023_pub02162023.pdf

"Focal, full-thickness (grade III or IV Outerbridge scale) **unipolar** lesions of the weight-bearing surface of the femoral condyles, trochlea, or patella that are at least 1.5 cm2 in size"

https://www.premera.com/medicalpolicies/7.01.48.pdf

Carelon:
"Lesion is discrete, single, and **involves only one side of the joint**"

"Condition involves a focal, full thickness, (grade III or IV) i**solated unipolar defect** of the knee involving the weight bearing surface of the medial or lateral femoral condyles or patellofemoral region (includes trochlear region, trochlear groove, and patella)"

From <https://guidelines.carelonmedicalbenefitsmanagement.com/joint-surgery-2023-11-05/>

From <https://guidelines.carelonmedicalbenefitsmanagement.com/joint-surgery-2023-11-05/>

These policies' requirement that a lesion be unipolar (and not bipolar) is supported by the summary on page 152 of the WA Health Technology Assessment Final Report on OATS from 2011, which found a high failure rate in bipolar grafts: "Unipolar versus bipolar grafts A case series of 123 patients (126 knees) found a significantly greater rate of graft failure in patients with grafts at both tibial and femoral sites (4/8; 50%) compared to patients with unipolar grafts (14/188; 12%; $p < 0.5$)". This topics was not addressed in the 2024 report specifically.

I note that some of the studies included in the 2024 evidence report evaluating the effectiveness of treatment of chondral defects excluded patients with bipolar lesions. This makes sense, as bipolar lesions have been considered relative contraindications to OATS and MACI procedures within the field of orthopedics (and typically not covered by health plans), and so these cases are not well-represented in the general literature regarding these procedures. Since the 2011 tech assessment, there have been more small case series reviewing the failure rates of bipolar restoration procedures, and those rates range from 0% to 50% based on the study (study sizes range from 12-60 patients). This data comes from a systematic review of rates of failure for cartilage restoration of bipolar lesions within the patellofemoral joint in 2021, which found only 237 knees with bipolar lesions meeting their inclusion/exclusion criteria in the 1,295 articles reviewed.

(Gowd AK, Weimer AE, Rider DE, Beck EC, Agarwalla A, O'Brien LK, Alaia MJ, Ferguson CM, Waterman BR. Cartilage Restoration of Bipolar Lesions Within the Patellofemoral Joint Delays Need for Arthroplasty: A Systematic Review of Rates of Failure. Arthrosc Sports Med Rehabil. 2021 Jun 14;3(4))

Therefore, I would appreciate the HTCC committee taking this failure rate and the local

coverage environment into account when finalizing the final coverage decision, and to please update the Limitations of Coverage to the following effect:

Change: "Symptomatic, single or multiple full-thickness (Outerbridge Classification of Grade III or IV) articular cartilage defects of the femoral condyle (medial, lateral, or trochlea) and/or patella"

To: "Symptomatic, single or multiple full-thickness (Outerbridge Classification of Grade III or IV) **unipolar** articular cartilage defects of the femoral condyle (medial, lateral, or trochlea) and/or patella".

Thank you very much for your consideration and the thoughtful work that has gone into this complex body of work.

Ty Jones, MD, CAQSM, CPPS, CPHQ (he/him)
Senior Medical Director support the Washington State Health Care Authority
Regence BlueShield WA
[redacted]

[redacted]