Washington State Health Care Authority

September 20, 2024 Meeting Materials
Health Technology Clinical Committee

Treatments for chondral defects of the knee

Contents

Health Technology Clinical Committee Application for Membership

Washington State Health Care Authority

1 Contact information

First name: Michael

Middle initial: G

Last name: James

Address:

Phone number:

Best method, time to reach you:

Email:

Today's date: 09/01/2024

2 Personal information (optional)

Gender:

✓ Male ☐ Female ☐ X/non-binary[1]

Pronouns (select all that apply)

☐ She/her ✓ He/him ☐ They/them ☐ Other (subj./obj.):

Race or Ethnicity

☐ American Indian or Alaska Native

☐ Asian or Pacific Islander American

☐ Black/ African American

☐ Latino, Hispanic, Spanish

✓ White/ Caucasian

☐ Other:

3 Professional training

Education (list degrees): MD, BS

Health care practitioner licenses: Oregon Medical License, Washington Medical License

Professional affiliations: Kaiser Permanente Northwest

Board certifications, formal training, or other designations: American Board of Orthopedic Surgery Eligible, Fellow of Royal College of Surgeons of Canada, Sports Medicine

Current position (title and employer): Sports Medicine Surgeon Kaiser Permanente Northwest

Current practice type and years in practice: Sports Medicine Surgeon

Total years as an active practitioner: 2

Location of practice (city): Salem, Portland Oregon

1 *Non-binary (X) is an umbrella term used to describe those who do not identify as exclusively male or female. This includes but is not limited to people who identify as genderqueer, gender fluid, agender, or bigender.*

4 Experience

Provide a brief explanation (up to 150 words each) addressing the following:

1) Why you would like to serve on the clinical committee;

I feel that my recent research endeavors can help inform the adoption of new techniques in Orthopedic Surgery

2) The value of informing health policy decisions with scientific evidence, including any examples incorporating new evidence into your practice;

I recently trained in an academic research institution and published several articles myself in the field of sports medicine. It is vital to stay up to date especially in the field of Sports Medicine for my daily practice.

3) How your training and experience will inform your role on the committee

I have expertise in Cartilage Restoration Techniques, ACL reconstruction and multiligamentous knee reconstruction and recently finished training at one of the top Sports Medicine Fellowships in the US.

4) Treating populations that may be underrepresented in clinical trials: women, children, elderly, or people with diverse ethnic and racial backgrounds, including recipients of Medicaid or other social safety net programs?

I treat many Medicaid patients in my practice and also trained in Canada, where we frequently serve underrepresented populations from very diverse ethnic backgrounds.

5 Ability to serve

Are you able to participate in all-day meetings, an estimated six times per year? ☐ Yes ☑ No

Are you willing to commit to the responsibilities of a committee member, including:

- Attending meetings prepared for the topics of the day;
- Actively participating in discussions;
- Making decisions based on the evidence presented and the public interest1? ☑ Yes ☐ No

Could you, or any relative, benefit financially from the decisions made by the HTCC? ☐ Yes ☑ No

6 References

Provide three professional references:

1.
First name: Michael
Last name: Hahn
Relationship: Supervisor
Title: Orthopedic Surgeon Kaiser
Contact email:
Phone number:

2.
First name: Nathan
Last name: Orvets
Relationship: Supervisor
Title: Head of Orthopedics Permanente Northwest
Contact email:
Phone number:

3.
First name: Matthew
Last name: Budge
Relationship: Partner
Title: Orthopedic Surgeon Kaiser
Contact email:
Phone number:

For your application to be reviewed, please include:

☑ Completed application ☑ curriculum vitae ☑ **conflict of interest disclosure**

Download this form and send the completed version to **shtap@hca.wa.gov**

OR mail to:
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

1 *Detailed in Washington Administrative Code (WAC) and committee bylaws*

MICHAEL G. JAMES MD, FRCSC, BSc

Orthopedic Surgeon

[redacted]

EMPLOYMENT

September 2023– Present	**Orthopedic Sports Medicine Surgeon** *Kaiser Permanente Northwest Oregon*
July 2022	**Orthopedic Surgeon** *Sea to Sky Orthopedics, Whistler/Squamish, BC*

EDUCATION

August 2022- July 2023	**Orthopedic Sports Medicine Fellowship** *University of Pittsburgh, Pittsburgh PA*
July 2017 – June 2022	**Orthopedic Surgery Residency Training Program** *Cumming School of Medicine, University of Calgary, Calgary AB*
August 2013 – May 2017	**Doctor of Medicine (MD)** *Washington University in St. Louis School of Medicine, St. Louis MO*
July 2009 – May 2012	**Bachelor of Science (BSc) Biology** *University of Winnipeg, Winnipeg MB*

EXAMINATIONS and CERTIFICATIONS

2023	ABOS Part 1
2022	Fellow of the Royal College of Physicians and Surgeons of Canada
2016– 2019	United States Medical Licensing Examination Step I, II CK/CS, III
2017-2019	Medical Council of Canada Qualifying Examination Part 1 and 2

RESEARCH

1. Lott A, **James MG,** Kaarre J, Höger S, Kayaalp ME, Ollivier M, Getgood A, Hughes JD, Musahl V. Around-the-knee osteotomies part II: Surgical indications, techniques and outcomes - State of the art. J ISAKOS. 2024 Apr 10:S2059-7754(24)00072-5. doi: 10.1016/j.jisako.2024.04.002. Epub ahead of print. PMID: 38604568.

2. Karimi A, Reddy RP, Njoku-Austin C, Nazzal E, **James MG**, Lin A. Reverse total shoulder arthroplasty for primary osteoarthritis with restricted preoperative forward elevation demonstrates similar outcomes but faster range of motion recovery compared to anatomic total shoulder arthroplasty. J Shoulder Elbow Surg. 2024 Jun;33(6S):S104-S110. doi: 10.1016/j.jse.2024.03.003. Epub 2024 Mar 12. PMID: 38485082.

3. **James MG**, Höger S, Musahl V. Editorial Commentary: Revision Meniscal Allograft Transplantation is a Bridge Option for Appropriately Indicated Patients With Realistic Patient Expectations in the Hands of Experienced Knee Surgeons Able to Perform All Necessary Concomitant Procedures. Arthroscopy. 2024 Feb;40(2):422-423. doi: 10.1016/j.arthro.2023.07.031. PMID: 38296445.

4. Reddy RP, Herman ZJ, Como M, **James MG**, Steuer FW, Adida S, Singh-Varma A, Nazzal EM, Njoku-Austin C, Karimi A, Lin A. Reversing chronic pseudoparesis secondary to massive, irreparable rotator cuff tear: superior capsular reconstruction vs. reverse total shoulder arthroplasty. J Shoulder Elbow Surg. 2024 Jun;33(6S):S16-S24. doi: 10.1016/j.jse.2023.10.026. Epub 2023 Dec 15. PMID: 38104716.

5. Özbek EA, Miller L, **James MG**, Mauro CS. Hip Capsular Closure in Distraction: A Technique to Allow Easier Closure of T and Interportal Capsulotomies. Arthrosc Tech. 2023 Jul 10;12(8):e1305-e1309. doi: 10.1016/j.eats.2023.03.023. PMID: 37654878; PMCID: PMC10466195.

6. Vergouwen M, **James MG**, You DZ, White NJ. Trends in implementation of evidence-based hip fracture management in a major Canadian city. OTA Int. 2023 Apr 25;6(2):e274. doi: 10.1097/OI9.0000000000000274. PMID: 37719312; PMCID: PMC10503671.

7. **James MG,** Kwong CA, More KD, LeBlanc J, Lo IKY, Bois AJ. Bony Apprehension Test for Identifying Bone Loss in Patients With Traumatic Anterior Shoulder Instability: A Validation Study. *The American Journal of Sports Medicine*. 2022;50(6):1520-1528. doi:10.1177/03635465221085673
8. **James M**, Dodd AE. Management of Deltoid Ligament Injuries in Acute Ankle Fracture: A Systematic Review. Canadian Journal of Surgery. 2022 Jan 11;65(1):E9-E15. doi: 10.1503/cjs.020320.
9. Lo A, **James MG**, Lo IKY. Arthroscopic Distal Tibial Allograft Reconstruction Using Double-Button Suture Fixation for Anterior Shoulder Instability with Glenoid Bone Loss. *360° Around Shoulder Instability.* R Brzoska, P Randelli, G Milano ed., Springer Press, 137-145, 2020.
10. Calgary Orthopaedic Resident Research Group (**James MG** included author). Quantification of Radiation Exposure in Orthopaedic Residents." *Orthopaedic Proceedings*. Vol. 102. No. SUPP_8. The British Editorial Society of Bone & Joint Surgery, 2020.
11. Calgary Orthopaedic Resident Research Group (**James MG** included author). Assessment of Radiation Safety Awareness Amongst Canadian Orthopaedic Surgery Residency Training Programs. *Journal of Graduate Medical Education*. 2020.

12. Killian, ML, **James, MG**, Thomopolous, S, and Clohisy, JC. A Novel Model for the Induction of Postnatal Murine Hip Deformity. *Journal of Orthopaedic Research.* 2018. DOI:10.1002/jor.24146

RESEARCH FUNDING

2022 **Albert B. Ferguson, Jr., M.D. Orthopedic Fund**
University of Pittsburgh, Pittsburgh PA
Long-term outcomes after medial meniscus root repair: a survival analysis
Value $10,000

2018 – 2020 **Calgary Orthopedic Research Education Fund Grant**
University of Calgary, Calgary, AB

1) Rate of Crossover from Non-Operative Treatment to Operative Fixation of Distal Radius Fractures ($5,000)
2) Quantification of Radiation Exposure in Orthopaedic Residents ($5,000)
3) Assessment of Radiation Safety Awareness Amongst Canadian Orthopaedic Surgery Residency Training Programs ($5,000)

2011-2012 **National Science and Engineering Research Council Undergraduate Research Awards**
Value $9000

AWARDS and SCHOLARSHIPS

2013-2017 **Washington University in St. Louis School of Medicine Scholarships**
School of Medicine Scholarship
Brown, Seymour and Rose Endowed Scholarship
Neilson, George and Elizabeth Scholarship
Scholars in Medicine Award
Dean's Fellowship
Guttman Scholarship

2012 **James Dorsett Scholarship for Excellence in Biology**
University of Winnipeg, Winnipeg, MB

2012 **Highest Academic Standing in Biology Undergraduate Degree (4.43/4.5 overall GPA)**
University of Winnipeg, Winnipeg, MB

2011/2012 ***Academic Proficiency Scholarship***
University of Winnipeg, Winnipeg, MB

Health Technology Clinical Committee Conflict of Interest Disclosure

Washington State Health Care Authority

Instructions

This conflict of interest (COI) form must be completed by an applicant for appointment to the state of Washington Health Technology Clinical Committee (HTCC) or clinical expert serving in a temporary capacity on the HTCC, as well as appointment to any of its subcommittees or work groups.

Those wishing to provide public comment at HTCC meetings are also requested to complete this COI form, but are not required to do so.

Instructions specific to HTCC applicants

As stewards of public funds, the practicing clinicians who serve (or apply to serve) on the Committee strive to uphold the highest standards of transparency and impartiality. Identifying financial, professional, and other interests contributes to the effective management of perceived, potential, and/or real conflicts of interest/bias that could affect Committee determinations (WAC 182-55). Management of potential conflicts of interest on specific topics are addressed in committee bylaws.

1 Applicant information

First name: Michael

Middle initial: G

Last name: James

Phone number:

Email:

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.

List amounts totaling $1,000 or more from a single source.

Indicate the category of financial interest/relationship by referring to the disclosure categories below. Select the letter corresponding to your financial interest(s). You may indicate multiple categories.

Indicate the source and date of the financial interest. For each chosen category, include date and if your activities are ongoing.

Indicate the recipient. Family: spouse, domestic partner, child, stepchild, parent, sibling (his/her spouse or domestic partner) currently living in your home.

Financial interest categories

Use these categories to indicate the nature of the financial interest:

A. Payment from parties with a financial or political interest in the outcome of work as part of your appointment or activity.

B. Employment including work as an independent contractor, consultant, whether written or unwritten.

C. Ownership or owning stock (stock, options, warrants) or holding debt or other significant proprietary interests or investments in any third party that could be affected.

D. Receiving a proprietary research grant or receiving patents, royalties, or licensing fees.

E. Participating on a company's proprietary governing boards.

F. Participating in a speakers bureau.

G. Receiving honoraria.

Please list your financial interests on the next page. Attach additional sheets if necessary.

Financial interest disclosures

Category (A-G)	Source of income and date	Amount	Recipient	
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family

3 Other interests

Please respond to the following questions. Disclose all interests that may apply to health technology assessment (HTA) topics covered in upcoming meetings.

Have you authored, coauthored, or publicly provided an opinion, editorial, or publication related to any meeting topic? Topic(s):

No

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topic(s):

No

Could a coverage determination based on a Committee topic conflict with policies you have promoted or are obliged to follow? Topic(s):

No

4 Signature

I have read the Conflict of Interest Disclosure form. I understand the purpose of the form and agree to the application of the information to determine conflicts of interest. The information provided is true and complete as of the date the form was signed. If circumstances change, I am responsible for notifying HTA program staff in order to amend this disclosure. I will complete this form annually by July 1st of each year of committee membership (*applies to HTCC committee only*).

To sign this request, do not use the "Fill & Sign" function; instead, simply click in the signature field to add your signature.

Signature

Date

09/01/2024

Download this form and send the completed version to **shtap@hca.wa.gov**.

Or mail to:
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

Treatments for Chondral Defects of the Knee

Ji Young Nam, MD, MPH
Associate Medical Director
Washington State Department of Labor and Industries
September 20, 2024

Washington State Health Care Authority

Background: Chondral Defects

- Damage of the surface cartilage lining the bones where they connect with other bones in synovial joints
- Articular cartilage has a limited ability to regenerate and is associated with scarring, progressive cartilage degeneration, and **increased risk for osteoarthritis** over time.
- Etiology: trauma, overuse, malalignment, osteochondritis dissecans, avascular necrosis, etc.
- True incidence is unknown with incidental findings of asymptomatic individuals.
- Symptoms: pain, catching or locking of the joint, swelling, impaired function, and impact on quality of life

Treatment for Chondral Defects of the Knee

- Microfracture (MF): often considered as **the "standard of care" comparator**
- Drilling
- Osteochondral autologous transplantation (OATS)
- Osteochondral allograft transplantation (OCA)
- Matrix-induced autologous chondrocyte implantation (MACI)

- If chondral defects progress to severe osteoarthritis, total knee replacement (TKR) may be necessary. To avoid TKR for patients younger than 55 years, these procedures can be considered.

Scope of the HTA

- Population: Individuals (any age) with chondral defects of the knee
- Intervention
  - Bone marrow stimulation procedures: MF and drilling
  - Osteochondral replacement: OATS and OCA
  - Cell-based restoration: MACI
- Outcomes
  - Patient-reported outcomes (PROs)
  - Rates of retreatment
  - Adverse events
  - Cost-effectiveness

Scope of the HTA (cont.)

- Comparator
  - Nonsurgical interventions, sham surgery, knee replacement, chondroplasty
  - For OATS, OCA: + MF or drilling
  - For MACI: + MF or drilling + OATS or OCA

- Excluded
  - First- and second-generation autologous chondrocyte implantation (ACI)
    - MACI is typically performed in contemporary clinical practice and has fewer complications.

2011 HTCC Review

- Topic: Osteochondral Allograft/Autograft Transplantation *(OATS/OCA)*

- HTCC Coverage determination
  - Osteochondral Allograft/Autograft is a **covered benefit with conditions**:
    - Age <50, older at the discretion of the agency;
    - Excluding malignancy, degenerative and inflammatory arthritis in the joint; and
    - Single focal full-thickness articular cartilage defect

  - Osteochondral Allograft/Autograft for joints other than knee is **not a covered benefit**

Agency Medical Director Concerns

Before

Efficacy = Medium

Safety = High

Cost = High

Now

Efficacy = Medium

Safety = Medium

Cost = High

Washington State Health Care Authority

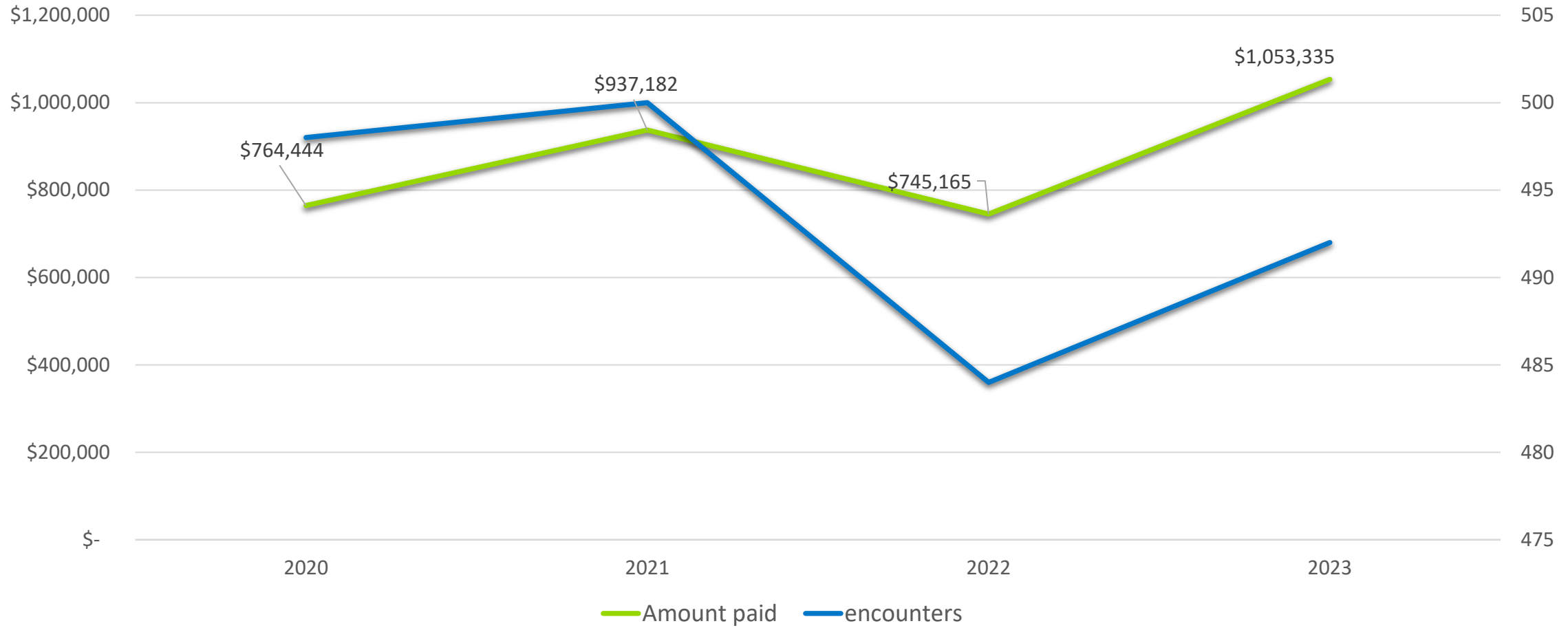
Key Questions

- Efficacy: What is the efficacy of the following cartilage defect treatments for chondral defects of the knee?
- Safety: What are the harms associated with treatments for chondral defects of the knee?
- Cost: What is the cost-effectiveness of treatments for chondral defects of the knee?

Current State Agency Policies

Procedures	ERB*/Uniform Medical Plan (UMP)	Medicaid	Labor and Industries
Microfracture/Drilling	No specific policy	No specific policy	Covered with conditions
OATS/OCA	Covered per HTCC determination	Covered per HTCC determination	Covered per HTCC determination
ACI/MACI	Covered with conditions	No specific policy (fee-for-service)	Not covered

Agency Combined Cost and Encounters: 2020-2023



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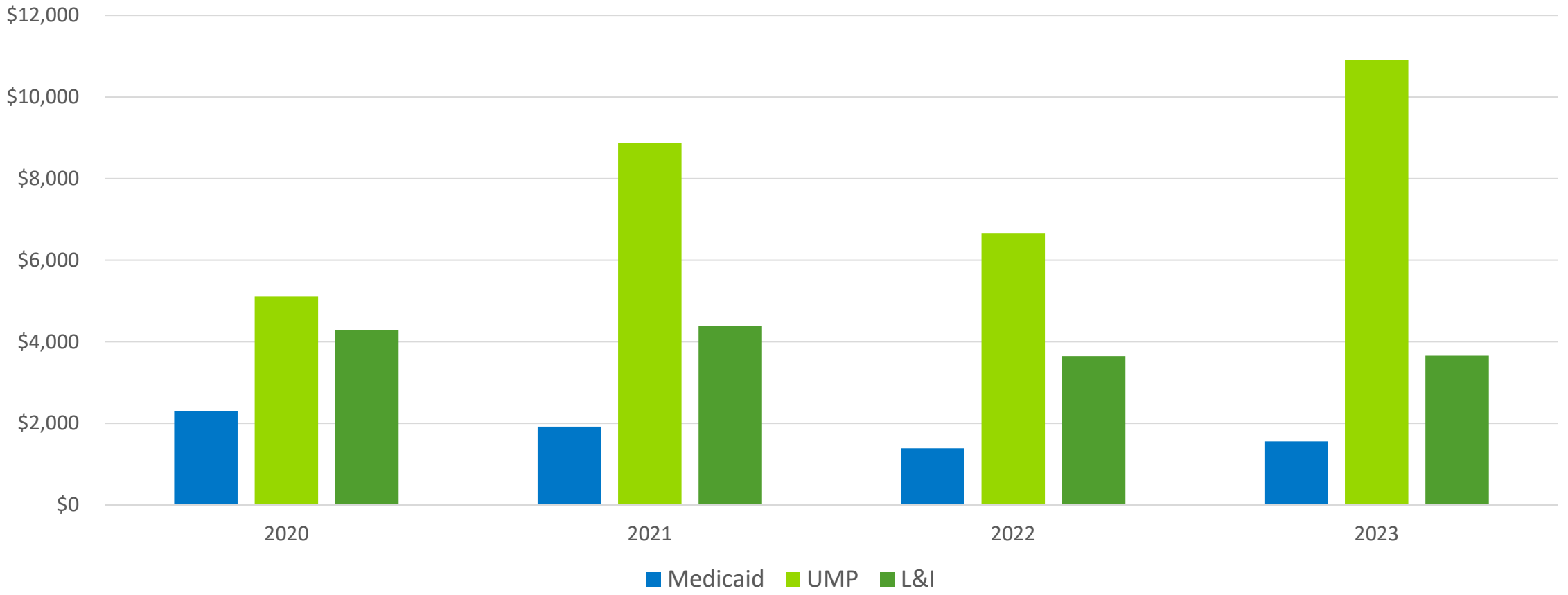
Average Payment Per Individual: 2020-2023



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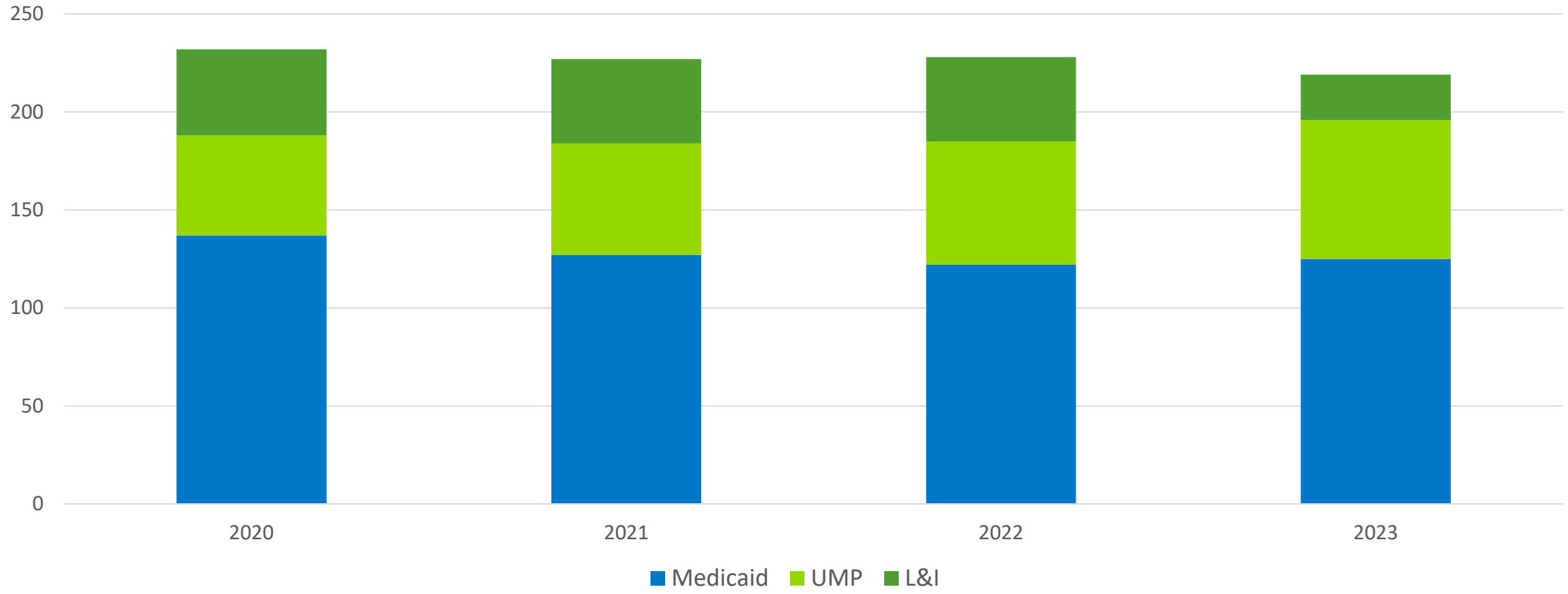
Individuals With At Least One Related Service: 2020-2023



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Efficacy: MACI

- MACI compared to MF: 3 RCTs, 2 NRSIs
  - 3 RCTs reported statistically and clinically significant improvements in PROs, with greater effectiveness of MACI compared with MF (moderate COE).
  - 2 RCTs reported greater response to MACI compared to MF (moderate COE).
  - 1 NRSI reported greater effectiveness of MACI (very low COE) and greater response to MACI compared to MF (low COE).
  - Follow up duration: 18-26 months in 4 studies and up to 5 years in 1 study

Summary of COE Ratings for MACI vs. MF

- PROs
  - Moderate COE for RCTs favors MACI
  - Very low COE for NRSIs favors MACI
- Response
  - Moderate COE for RCTs favors MACI
  - Low COE for NRSIs favors MACI
- Re-operation
  - Low COE for RCTs: Comparable
  - Very low COE for NRSIs favors MACI
- Treatment failure
  - Low COE for RCTs: Comparable
  - Very low COE for NRSIs: Comparable

Evidence Considerations: MACI

- Findings consistently showed favorable outcomes (PROs, response) of MACI compared to MF from 3 RCTs and 2 NRSIs.

- Moderate COE rating for RCTs on PROs and response, But…
  - Small sample size
  - Differing patient selection criteria
  - Industry funding: 2 RTCs were funded entirely by industry

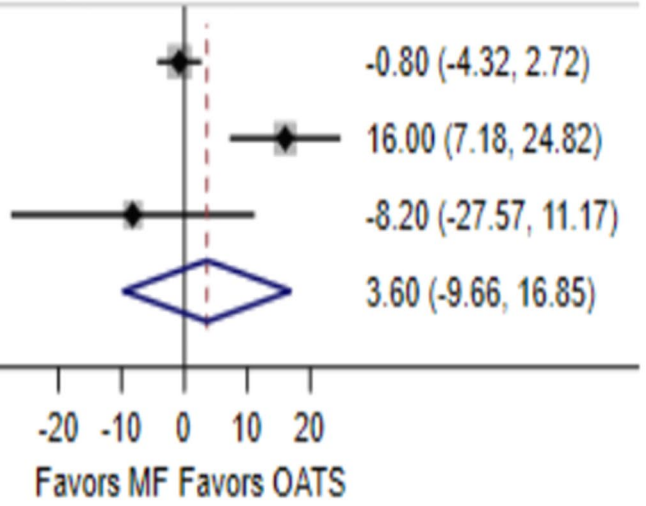
Efficacy: OATS, OCA

- OATS compared to Bone Marrow Stimulation Procedures: 5 RCTs, 2 NRSIs
  - OATS and MF groups reported similar improvements in PROs (low COE in RCTs, very low COE in NRSIs).
  - One RCT (n=40) reported greater response to treatment for the OATS group compared to the MF group (low COE).
  - Treatment failure was lower for OATS for 3 RCTs (very low COE) and 1 NRSI (low COE).
  - Mean follow-up duration varied from 2 years to more than 10 years.
- OCA compared to OATS: 2 NRSIs
  - Studies reported no statistically significant differences in need for any reoperation between OCA and OATS (low COE).

Efficacy: OATS (cont.)

Figure 4. Meta-analysis of OATS Compared to MF Using Lysholm Score

Author, Year	Mean age years (range)	Mean defect size cm^2 (range)	Follow-up Time (years)	Risk of Bias	Sample Size	Mean difference (95% CI)
Lim, 2012	30 - 33	2.7 - 2.8	5	High	47	-0.80 (-4.32, 2.72)
Solheim, 2018	31 - 35	3.4 - 3.5	5	SC	40	16.00 (7.18, 24.82)
Ulstein, 2014	32 - 33	2.6 - 3.0	10	SC	25	-8.20 (-27.57, 11.17)
Overall, DL (I^2 = 84.6%, p = 0.002)						3.60 (-9.66, 16.85)



- Small sample size
- Differing patient selection criteria

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Summary of COE Ratings for OATS vs. MF

- PROs
  - Low COE for RCTs: Comparable
  - Very low COE for NRSIs: Comparable
- Response
  - Low COE for RCTs favors OATS
- Re-operation
  - Very low COE for RCTs: Comparable
- Treatment failure
  - Very low COE for RCTs favors OATS
  - Low COE for NRSIs favors OATS

First-line vs. Second-line Procedures (MACI and OCA)

- First-line MACI vs. Second-line MACI: 1 NRSI
- First-line OCA vs. Second-line OCA: 3 NRSIs

- First-line MACI procedures reported greater improvement in PROs compared to second-line MACI (very low COE); PRO results for first-line and second-line OCA were similar (very low COE).
- Fewer treatment failures and re-operations for first-line MACI and OCA procedures compared to second-line MACI and OCA procedures (very low COE).

Evidence: Cell-free Implants

- Cell-free aragonite implants (Agili-C) vs. MF/Chondroplasty: 1 RCT (n=251)
  - Greater improvement in PROs and response in the cell-free implant group compared to MF/chondroplasty (moderate COE).

- Evidence considerations: High risk of bias
  - Lack of information in randomization domain
  - Baseline differences in disease severity
    - Mild/moderate OA based on KL grade: 45.5% on Agili-C, 64.3% in control group
  - Lack of long-term clinical data
  - One septic arthritis (0.6%) in Agili-C group
  - Agili-C: FDA Breakthrough device status, 2022

Evidence: AMIC

- Autologous Matrix-Induced Chondrogenesis (AMIC) vs. MF: 1 RCT
  - Cincinnati Knee Rating System improved at 1 year for AMIC and MF groups;at 5 years follow-up, improvement sustained in the AMIC groups only while the MF group experienced a score degradation (low COE).

- Evidence considerations: High risk of bias
  - Low sample size (n=47)
  - No intention to treat analysis
  - Missing outcome data
  - Non-blinded assessment of the outcome
  - Funded entirely by industry
  - Chondro-gide: FDA Breakthrough device status, 2021

Safety

- Limited number of studies reported harms.
- When they were reported, the COE was low or very low due to **few events** and high risk of bias in the evidence base.
- Common AEs included knee pain and joint swelling.
- SAEs included deep vein thrombosis, septic arthritis, and muscle atrophy.

- Based on available evidence, reported AE and SAE events from MACI and OATS are mostly comparable to MF.

Costs/Cost-effectiveness

- No evidence for MACI compared to other procedures.
- MACI: 2-stage surgical procedure, longer rehabilitation period

- *Microfracture and osteochondral autograft transplantation are cost-effective treatments for articular cartilage lesions of the distal femur* (Miller et al., Am J Sports Med. 2015)
  - Only 1 eligible study with U.S.-based cost inputs derived from a single institution (unable to determine COE).
  - For most sensitivity analyses, the total costs for OATS and MF were equivalent.
  - Based on return to play outcome, OATS appears to be more cost-effective at 1, 3, and 10 years of follow-up.

Other Payers' Policies

No CMS national coverage determinations for chondral defect treatment procedures

Table 28. Select Overview of Payer Coverage Policies for Chondral Defect Repair of the Knee

Condition	Medicare	Cigna[85]	Kaiser Permanente	Premera Blue Cross[86,87]	Regence BlueShield[88]	UnitedHealth[89]
Microfracture	—	—	—	—	—	✓
Drilling	—	—	—	—	—	—
OATS	—	✓	—	✓	—	✓
OCA	—	✓	—	✓	—	✓
ACI/MACI	—	✓	—	✓	✓	✓

Notes: ✓ = covered; X = not covered; — = no policy identified.

Abbreviations: ACI = autologous chondrocyte implantation; MACI = matrix-induced autologous chondrocyte implantation; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation.

Guidelines

- No clinical practice guideline for MACI.

- Mosaicplasty for symptomatic articular cartilage defects of the knee: NICE (2018)
  - Mosaicplasty including OATS: Evidence of the safety and efficacy is adequate to support the use of the procedure.
  - The procedure should only be done by surgeons experienced in cartilage surgery and who have specific training in mosaicplasty for knee cartilage defects.

Agency Medical Directors Recommendations

- 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 and inflammatory arthritis in the joint

Agency Medical Directors Recommendations (cont.)

- 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 arebetween 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 and inflammatory arthritis in the joint

Agency Medical Directors Recommendations (cont.)

- Cell-free implants and AMIC are not a covered benefit.

Questions?

More Information:

Ji Young Nam, MD, MPH
namj235@lni.wa.gov

Washington State Health Care Authority

Addendum

Table 1. Indications for Chondral Defect Repair Procedures by Size and Subchondral Involvement[63]

Procedure	Size of defect	Subchondral involvement
Chondroplasty	< 2 cm^2	No
Microfracture/drilling	< 4 cm^2	No
Osteochondral autologous transplantation (OATS)	2 cm^2 to 4 cm^2	Yes
Osteochondral allograft transplantation (OCA)	> 4 cm^2	Yes
Matrix-induced autologous chondrocyte implantation (MACI)	> 4 cm^2	Minimal

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

Outerbridge Arthroscopic Grading System

	Slattery and Kweon, Clin Orthop Relat Res (2018)
Grade 0	Normal cartilage
Grade I	Softening and swelling (noted with tactile feedback with probe)
Grade II	Partial-thickness defect with surface fissures (do not reach subchondral bone or exceed 0.5 inches in diameter)
Grade III	Deep fissures at the level of subchondral bone with a diameter > 0.5 inches
Grade IV	Exposed subchondral bone

Table 5. Summary of Validated Measures Reported by Included Studies

Instrument	Description	Score Range; Directionality of Scale	Entity Completing Survey	Minimal Clinically Important Difference or Clinically Relevant Thresholds
Outcome Focus: Symptoms and Function				
Cincinnati Knee Rating System (CKRS)	8 questions in 3 domains measuring symptoms, function, and activities of daily living	0 to 100; higher scores indicate fewer symptoms and greater function	Patient	Unknown
Hospital for Special Surgery (HSS) Knee Rating Scale	Evaluates categories of pain, function, range of motion, muscle strength, flexion deformity, and instability	0 to 100; higher scores indicate fewer symptoms and greater function	Clinician	Excellent ≥ 85 Good = 70 to 84 Fair = 60 to 69 Poor ≤ 60[73]
International Knee Documentation Committee (IKDC) Subjective Score	Detects change in symptoms, function, and sports activities due to knee impairment	0 to 100; higher scores indicate fewer symptoms and greater function	Patient	Range: 6.3 to 16.7[74]
Knee Injury and Osteoarthritis Score (KOOS) Subscales	Rating of 5 domains: (1) pain; (2) knee symptoms; (3) performance of ADLs; (4) sports and recreational activities; (5) QOL	0 to 100; higher scores indicate fewer symptoms and greater function	Patient	Pain: 8.0 to 16.7 Symptoms: 2.5 to 10.0 ADL: 3.7 to 10.0 Sport:12.0 to 25.0 QOL: 3.7 to 9.3[75]
Lysholm score	Subscales for pain, instability, locking, swelling, limp, stair climbing, squatting, and need for support	0 to 100; higher scores indicate fewer symptoms and greater function	Patient	3.7 to 12.0[74,75] Categories[76] 95 to 100 = Excellent 84 to 94 = Good 65 to 83 = Fair < 65 points= Poor
Outcome Focus: Function				
Tegner Score[74]	Describes the level of work- and sports-based activity in which a patient can engage	0 to 10; higher scores indicate greater function	Patient	0: sick leave 5: return to work 7: return to recreational sports 10: return to high-impact sports

Abbreviations: ADL = activities of daily living; QOL = quality of life.

Washington State Health Care Authority

Treatments for chondral defects of the knee

Order of scheduled presentations:

	Name
1	**Smith+Nephew** • Carolyn Garziano, DPT • Steven Moore
2	**Vericel** • Andrew Kocher, DPT

Health Technology Clinical Committee Conflict of Interest Disclosure

Washington State Health Care Authority

Instructions
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1 Applicant information

First name: Michael

Middle initial: G

Last name: James

Phone number:

Email:

2 Financial interests

Disclose your financial interests and relationships occurring over the last twenty-four months.
List amounts totaling $1,000 or more from a single source.
Indicate the category of financial interest/relationship by referring to the disclosure categories below. Select the letter corresponding to your financial interest(s). You may indicate multiple categories.
Indicate the source and date of the financial interest. For each chosen category, include date and if your activities are ongoing.
Indicate the recipient. Family: spouse, domestic partner, child, stepchild, parent, sibling (his/her spouse or domestic partner) currently living in your home.

Financial interest categories

Use these categories to indicate the nature of the financial interest:

A. Payment from parties with a financial or political interest in the outcome of work as part of your appointment or activity.
B. Employment including work as an independent contractor, consultant, whether written or unwritten.
C. Ownership or owning stock (stock, options, warrants) or holding debt or other significant proprietary interests or investments in any third party that could be affected.
D. Receiving a proprietary research grant or receiving patents, royalties, or licensing fees.
E. Participating on a company's proprietary governing boards.
F. Participating in a speakers bureau.
G. Receiving honoraria.

Please list your financial interests on the next page. Attach additional sheets if necessary.

Financial interest disclosures

Category (A-G)	Source of income and date	Amount	Recipient	
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family

3 Other interests

Please respond to the following questions. Disclose all interests that may apply to health technology assessment (HTA) topics covered in upcoming meetings.

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No

Are you involved in formulating policy positions or clinical guidelines related to any meeting topic? Topic(s):

No

Could a coverage determination based on a Committee topic conflict with policies you have promoted or are obliged to follow? Topic(s):

No

4 Signature

I have read the Conflict of Interest Disclosure form. I understand the purpose of the form and agree to the application of the information to determine conflicts of interest. The information provided is true and complete as of the date the form was signed. If circumstances change, I am responsible for notifying HTA program staff in order to amend this disclosure. I will complete this form annually by July 1st of each year of committee membership (*applies to HTCC committee only*).

To sign this request, do not use the "Fill & Sign" function; instead, simply click in the signature field to add your signature.

Signature

Date

09/01/2024

Download this form and send the completed version to **shtap@hca.wa.gov**.

Or mail to:
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

Overview Summary

- Excellent review of technology
- Identifies gaps still to be addressed
  - Evidence development
  - Unmet clinical needs
- Appreciate the review and opportunity to comment

Technology Description

Table ES-1. Indications for Chondral Defect Repair Procedures by Size and Subchondral Involvement[13]

Procedure	Size of defect	Subchondral involvement
Chondroplasty	< 2 cm2	No
Microfracture/drilling	< 4 cm2	No
Osteochondral autologous transplantation (OATS)	2 cm2 to 4 cm2	Yes
Osteochondral allograft transplantation (OCA)	> 4 cm2	Yes
Matrix-induced autologous chondrocyte implantation (MACI)	> 4 cm2	Minimal

Procedure	Size of Defect	Subchondral Involvement	Presence of OA
Chondroplasty	$<2cm^2$	No	Yes
Microfracture Drilling	$<4cm^2$	No	Yes
Osteochondral autologous transplantation (OATS)	$2cm^2$ to 4 cm^2	Yes	None to Minimal
Osteochondral allograft transplantation (OCA)	>4 cm^2	Yes	None to Minimal
Matrix-induced autologous chondrocyte implantation (MACI)	$>4cm^2$	Minimal	None to Minimal
Cell-Free Implant (CartiHeal Agili-C)	*$2cm^2$ to $10cm^2$*	*Yes*	*None to Moderate*

- Indications do not include emerging implant technology beyond auto/allografts
- Unmet needs remain:
  - Address defects $>4cm^2$with subchondral involvement
  - Address defects $<4cm^2$ with subchondral involvement
  - Presence & degree of OA in surrounding cartilage
  - Sourcing and tissue matching barriers
  - Time & Cost

CartiHeal Agili-C Cell Free Cartilage Repair Implant

- 251 patient RCT
- Moderate confidence of evidence for effectiveness in PROs and Responder – same as MACI
- 4-year manuscript submitted
- 5-year data complete and in process
- Compelling evidence worthy of consideration as a treatment option in select patients while more evidence is developing
- Addresses unmet need for chondral defects from 2-10cm^2 with subchondral involvement
- Addresses unmet need for chondral defects in the presence of OA up to moderate
- One-step, cost-effective procedure absent sourcing or tissue matching barriers

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Washington State Health Care Authority

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[redacted]icant information

First name: Andrew

Middle initial: P

Last name: Kocher

Phone number:

Email:

[redacted]ncial interests

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Financial interest disclosures

Category (A-G)	Source of income and date	Amount	Recipient	
	Employee and stockholder of Vericel		X	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family
			Self	Family

3 Other interests

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Signature

Date

9/5/2024

Download this form and send the completed version to **shtap@hca.wa.gov**.

Or mail to:
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

MACI Clinical Overview

MACI® is regulated by the FDA as a Combination Product: CBER – BLA: 351 Product

MACI® is an autologous cellularized scaffold product indicated for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults.

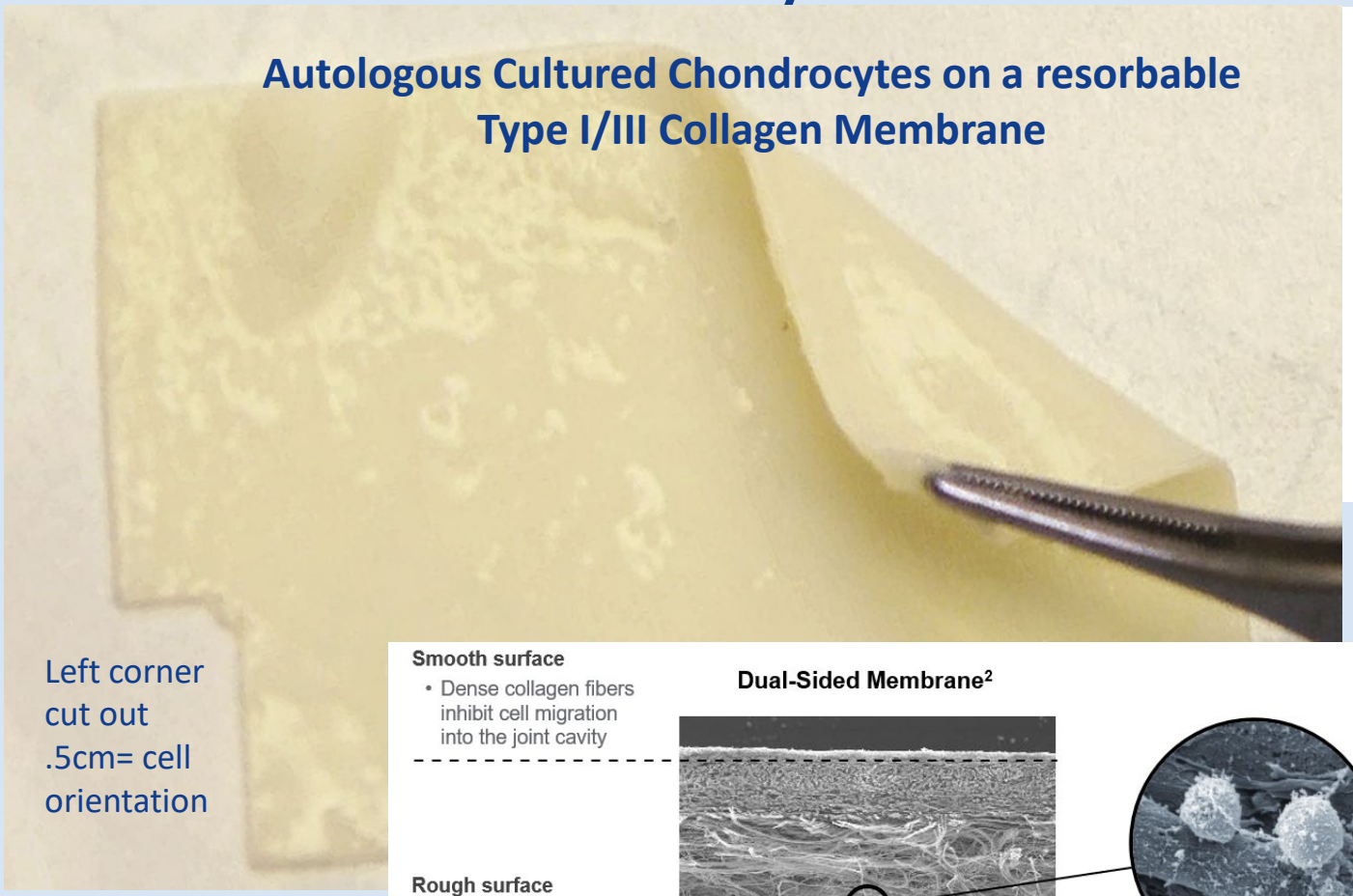
MACI® is the first FDA-approved product that applies the process of tissue engineering to grow cells on scaffolds using healthy cartilage tissue from the patient's own knee. (FDA News Release: December 13, 2016)

VERICEL

MACI [prescribing information]. Cambridge, MA: Vericel Corporation; June 2021. [2]Zheng MH, et al. *Tissue Eng*. 2007;13(4):737-746

Manufactured in Accordance With Quality GMP Standards in an FDA-Licensed Facility[1,2]

Autologous Cultured Chondrocytes on a resorbable Type I/III Collagen Membrane



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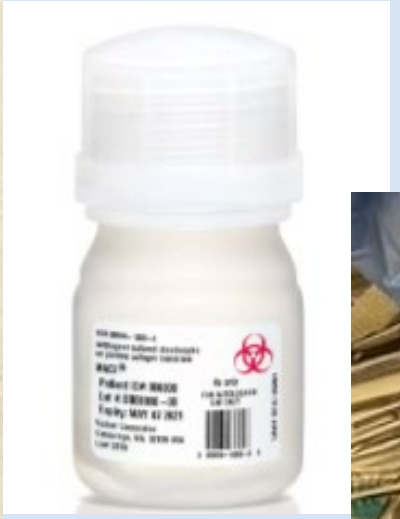

Savillex Bottle

Picture courtesy of James Cary, UPENN

MACI [prescribing information]. Cambridge, MA: Vericel Corporation; June 2021. [2]Zheng MH, et al. *Tissue Eng*. 2007;13(4):737-746

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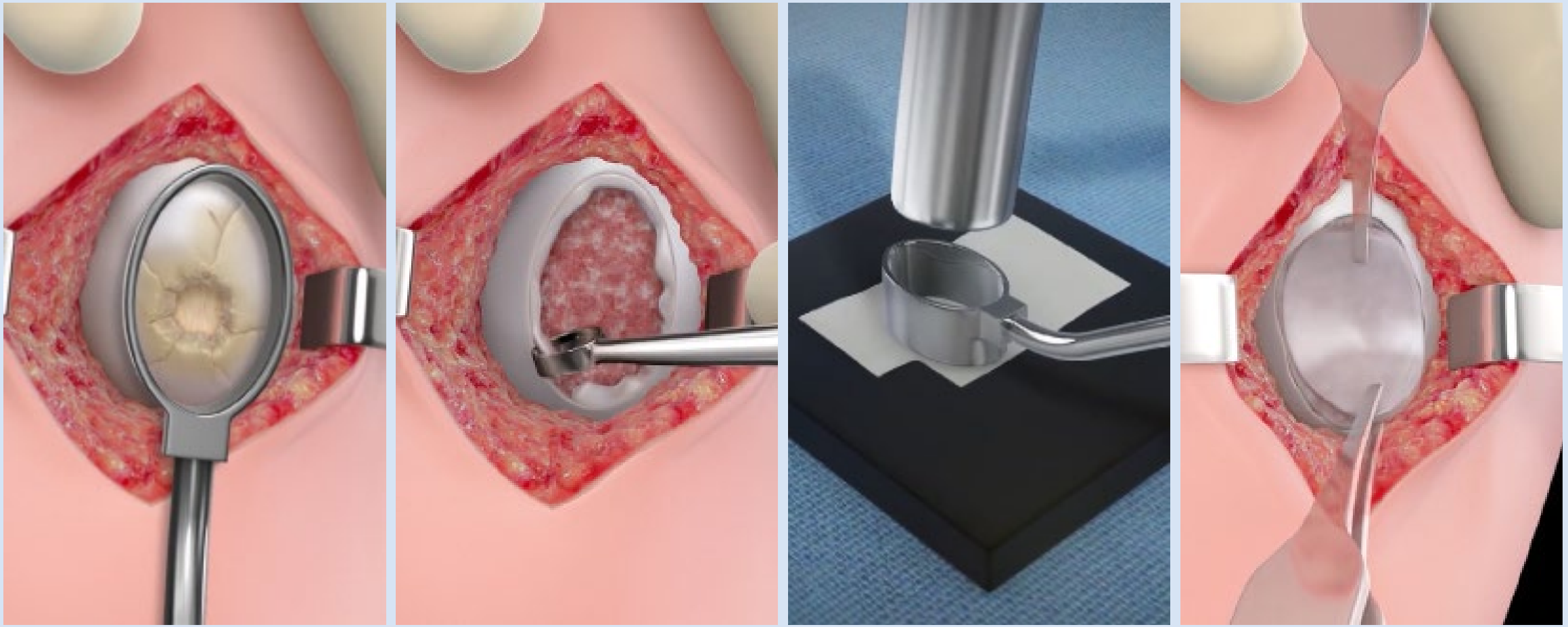
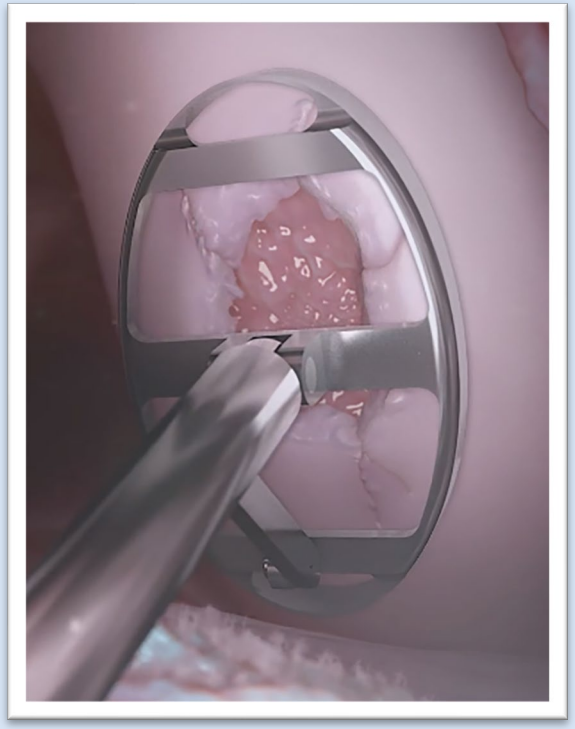
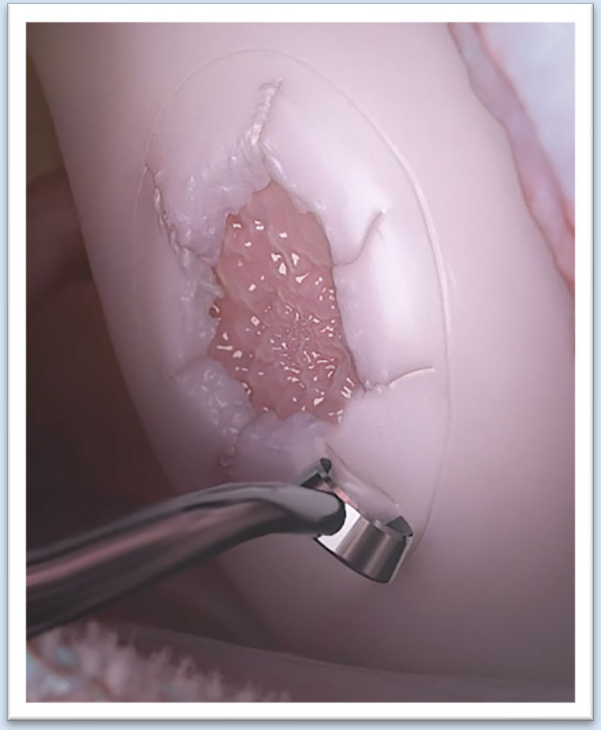
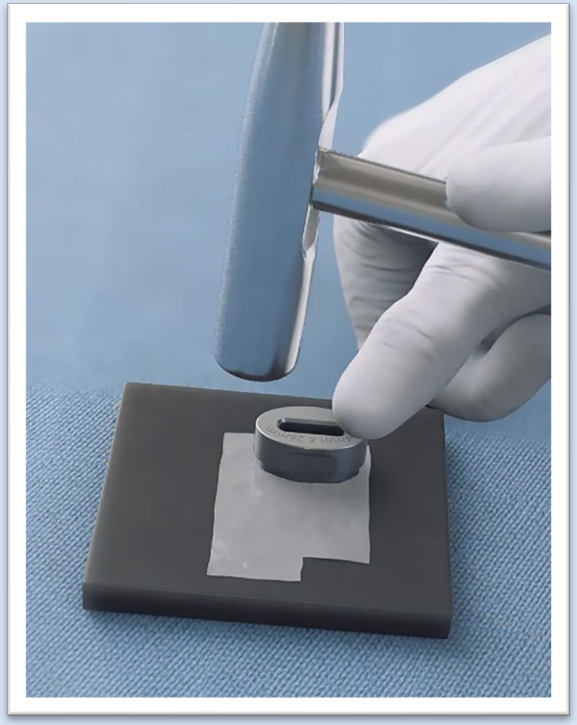
MACI Surgical Procedure: Arthrotomy

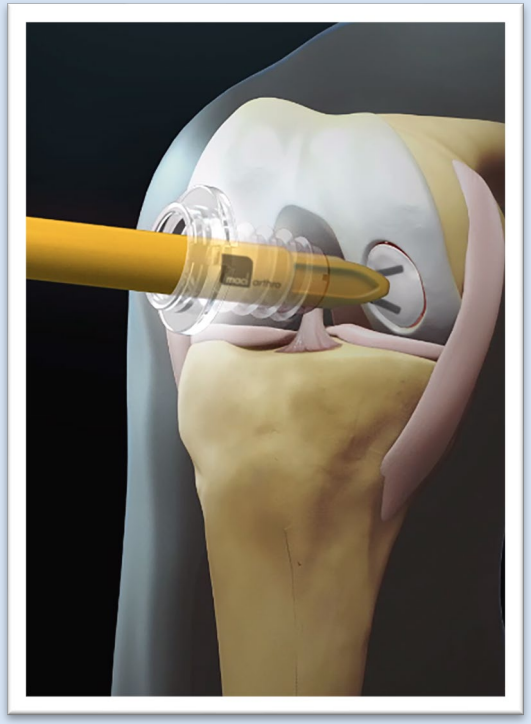


MACI Surgical Procedure: Arthroscopy









Required Clinical Standards: Randomized Control Superiority Trial

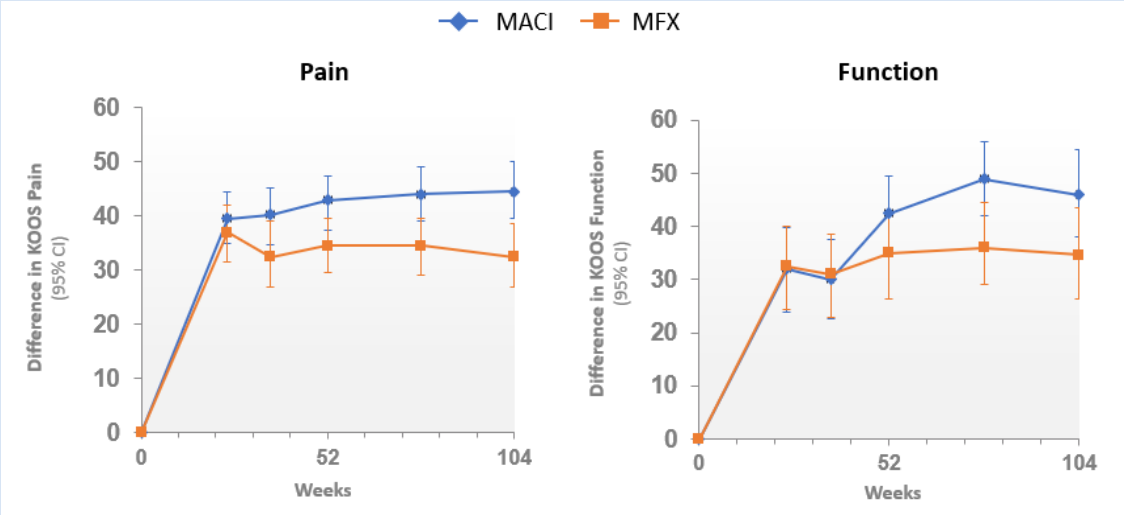
Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture

Two-Year Follow-up of a Prospective Randomized Trial

Daniel Saris,[*†‡] MD, PhD, Andrew Price,[§] MD, Wojciech Widuchowski,[‖] MD, PhD, Marion Bertrand-Marchand,[¶] MD, Jacob Caron,[#] MD, Jon Olav Drogset,[**] MD, PhD, Pieter Emans,[††] MD, PhD, Ales Podskubka,[‡‡] MD, PhD, Anika Tsuchida,[†] MD, Sven Kili,[§§] MD, David Levine,[‖‖] MD, MPH, and Mats Brittberg,[¶¶] MD, PhD, on behalf of the SUMMIT study group[##]

Investigation performed at several sites sponsored by Sanofi

MACI demonstrated to be safe and effective based on superior clinical outcomes over MFX: Primary End Points- Pain & Function



Saris D, et al. The American Journal of Sports Medicine 2014 42

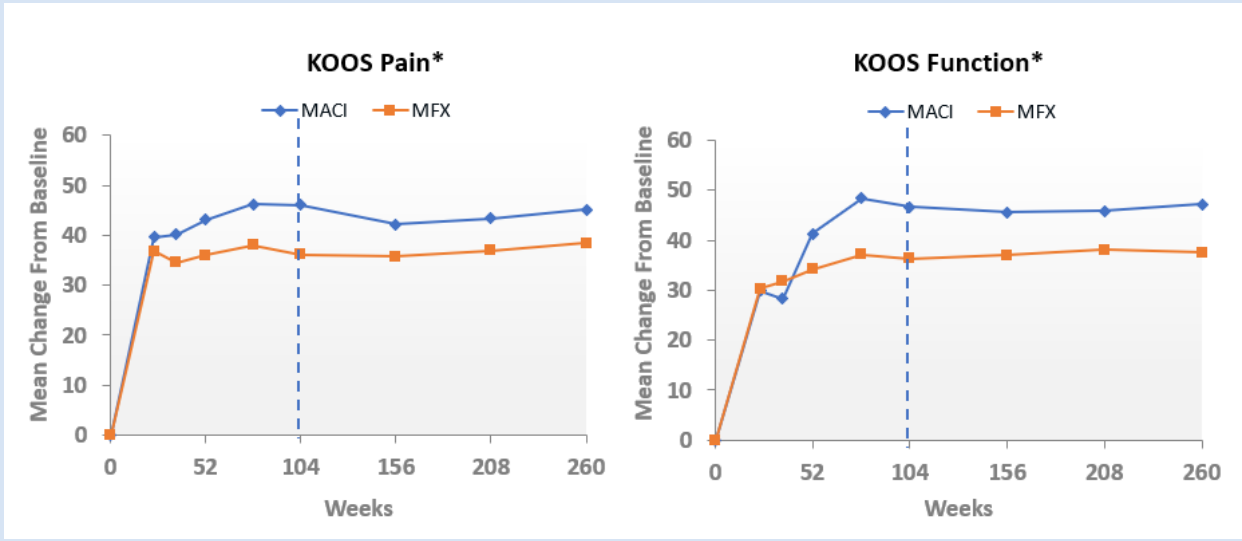
Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture

Five-Year Follow-up of a Prospective Randomized Trial

Mats Brittberg,[*†] MD, PhD, David Recker,[‡] MD, John Ilgenfritz,[§] PhD, and Daniel B.F. Saris,[*‖¶#] MD, PhD, on behalf of the SUMMIT Extension Study Group[**]

Investigation performed by the SUMMIT Extension Study Group based on the multicenter study performed at 14 sites across 7 European countries

The clinical outcomes over MFX seen at 2yrs were maintained at 5yrs



Brittberg M et al. The American Journal of Sports Medicine 1–9 2018

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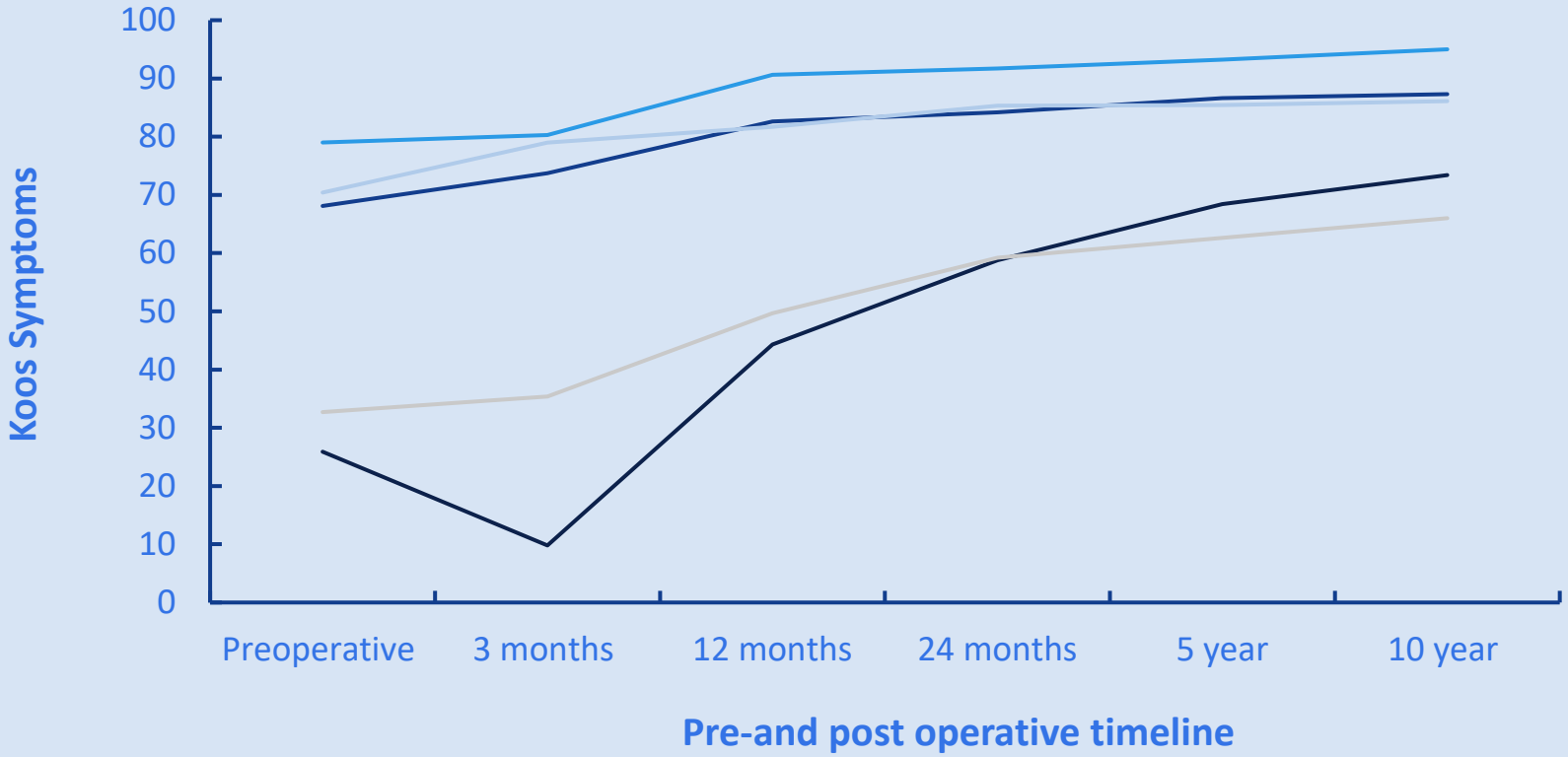
10 Year Clinical Outcomes with MACI

Clinical effect achieved at five years was sustained out to 10 years



Patient Satisfaction 10yrs

- Pain – 93%
- ADL – 95%
- Rec Act – 90%
- Sports – 83%
- Overall – 88%

Ebert JR, Fallon M, Ackland TR, Janes GC, Wood DJ. Minimum 10-Year Clinical and Radiological Outcomes of a Randomized Controlled Trial Evaluating 2 Different Approaches to Full Weightbearing After Matrix-Induced Autologous Chondrocyte Implantation. *Am J Sports Med*. 2020;48(1):133-142.

VERICEL

11-16-Year Prospective Follow-up Data

Long-term Prospective Clinical and Magnetic Resonance Imaging–Based Evaluation of Matrix-Induced Autologous Chondrocyte Implantation

Jay R. Ebert,*†‡ PhD, Michael Fallon,§ MBBS, David J. Wood,‖ BSC MBBS, MS, and Gregory C. Janes,¶ MBBS
Investigation performed at the University of Western Australia, Perth, Australia

(2021). *American Journal of Sports Medicine*.

- Prospective case series
  - 87 patients (99 grafts)
  - 81 TF, 18 PF
  - Pre-surgery & 2, 5, 10 and **11-16 years**

Significant improvements in all PROM's, objective scores & MRI-based outcomes measures (9.1%) Graft Failure
Overall Patient Satisfaction: 88%
KOOS Sports Score: 75

MACI provided high levels of satisfaction and graft survivorship as visualized on MRI at 11 to 16 years after surgery.

Objective Assessment: Functional Strength

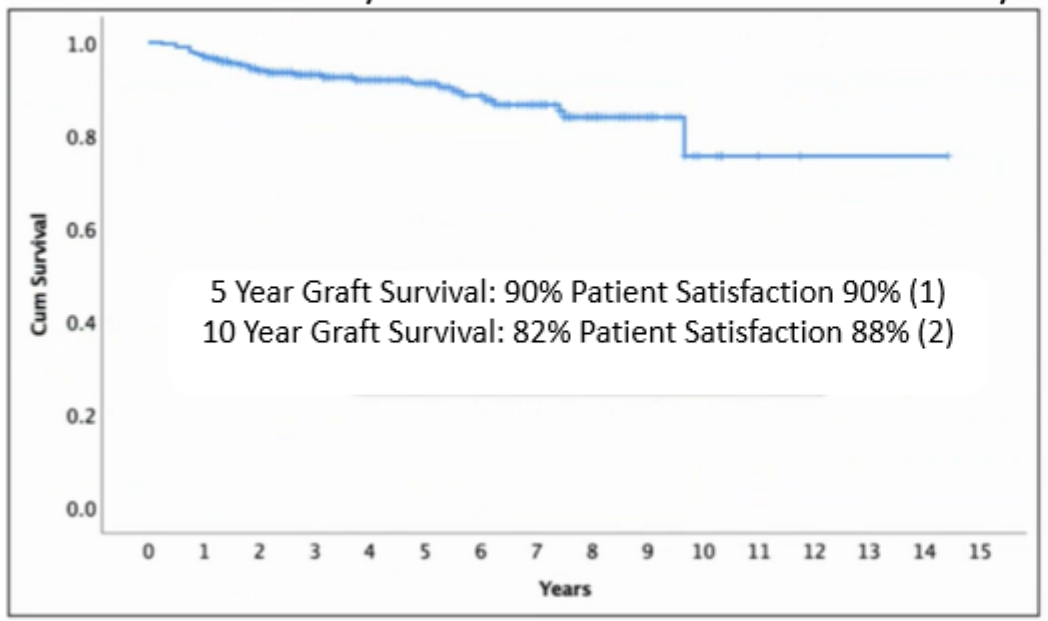
Significant Improvement in KOOS Sports and Quad Strength Strength LSI from Five Years to Final Follow-up

Objective	Mean (SD)	% of Patients with LSI >90%
Single hop for distance	95.5 (73-116)	85.7%
Triple hop for distance	96.7 79.8 111.3	86.8%
Knee extension peak torque (Nm)	96.8 75.8-122	77.3%
Knee flexion peak torque (Nm)	96.9 80-125	88.8%

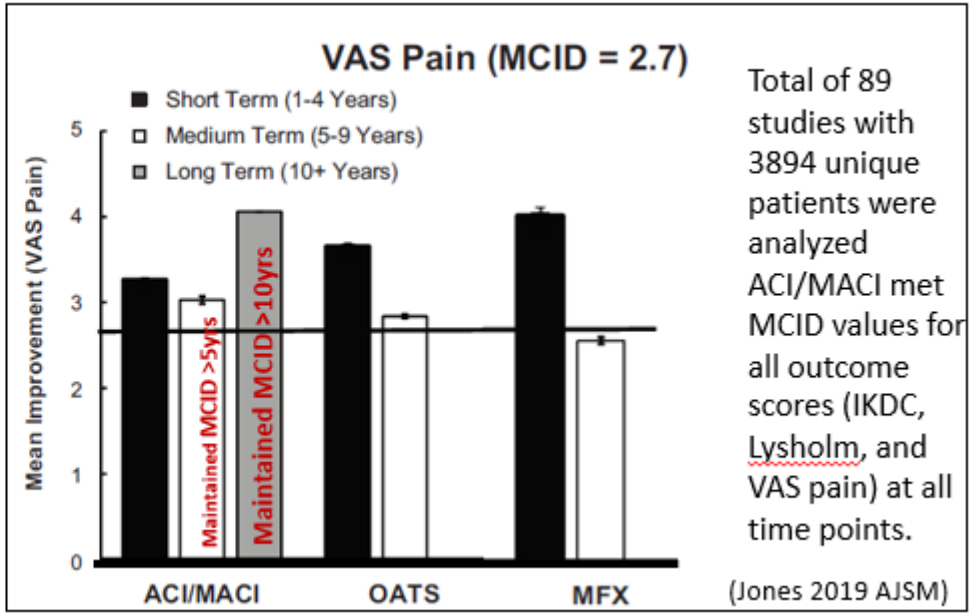
Grading	Pain	Undertake ADL	Participating in Rec Activities	Participating in Sports	Overall Satisfaction
Very Satisfied	50	49	45	25	49
Satisfied	31	32	28	40	28
Dissatisfied	5	5	8	7	8
Very Dissatisfied	1	1	6	15	2
Combination Very Satisfied and Satisfied Scores	81 (93.1)	81 (93.1%)	73 (83.9%)	65 (74.7%)	77 (88.5%)

Clinically Meaningful Pain Relief and Patient Satisfaction

MACI: Survival Analysis and Patient Satisfaction: 5 to 10yrs



MACI: Minimal Clinically Important Differences: 5 to 10yrs



Total of 89 studies with 3894 unique patients were analyzed ACI/MACI met MCID values for all outcome scores (IKDC, Lysholm, and VAS pain) at all time points.

(Jones 2019 AJSM)

1 Ebert, J., Robertson, W., Woodhouse, J. J., Fallon, M., Zheng, M., Ackland, T. & Wood, D., Clinical and Magnetic Resonance Imaging-Based Outcomes to 5 Years After Matrix-Induced Autologous Chondrocyte Implantation to Address Articular Cartilage Defects in the Knee. The American Journal of Sports Medicine. 2011 39, 4, p. 753-763

2 Ebert, J. R., Fallon, M., Ackland, T. R., Janes, G. C., & Wood, D. J. (2019). Minimum 10-Year Clinical and Radiological Outcomes of a Randomized Controlled Trial Evaluating 2 Different Approaches to Full Weightbearing After Matrix-Induced Autologous Chondrocyte Implantation. *American Journal of Sports Medicine*.

3. Jones, K et al. Comparative Effectiveness of Cartilage Repair With Respect to the Minimal Clinically Important Difference. Am J Sports Med 2019 Nov;47(13):3284-3293.

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MACI Cost Efficacy

TABLE 5
Cost per QALY Over 10 Years in Base Model and With Sensitivity Analysis[a]

		Costs				Efficacy[b]		Failure Rate[c]	
Initial Therapy	Base Model	–50%	–25%	+25%	+50%	+MCID	–MCID	+10%	+15%
ACI-P	18,490	9245	13,868	23,113	27,735	11,274	**51,379**	20,643	21,759
Patella	15,133	7567	11,350	18,917	22,700	9954	31,551	17,114	18,162
MACI	17,534	8767	13,150	21,917	26,301	11,218	40,122	19,693	20,833
Microfracture									
<3 cm^2	6808	3404	5106	8510	10,212	4383	15,238	8522	9423
>3 cm^2	14,568	7284	10,926	18,210	21,852	7724	**127,782**	16,588	17,572
OAT									
1 or 2 plugs	7370	3685	5527	9212	11,054	4768	16,224	9075	9971
3 or 4 plugs	12,884	6442	9663	16,105	19,326	8255	29,331	14,937	16,029
OCA	19,911	9956	14,933	24,889	29,867	12,713	45,899	22,140	23,314
Bipolar lesion	27,081	13,540	20,311	33,851	40,621	17,019	**66,255**	30,232	31,944
Patella	24,725	12,363	18,544	30,907	37,088	15,161	**66,975**	27,302	28,659

[a]All values are given in US dollars. Bold values indicate cost-inefficacy. ACI-P, autologous chondrocyte implantation with periosteum cover; IKDC-S, International Knee Documentation Committee subjective form; MACI, matrix-induced autologous chondrocyte implantation; MCID, minimum clinically important difference; OAT, osteochondral autograft transfer; OCA, osteochondral allograft; QALY, quality-adjusted life-year.
[b]Defined as 16.7 points on the IKDC-S scale for patients with symptomatic cartilage defects.
[c]Increased failure rate of the initial procedure only.

MACI remained cost-effective through the modeled scenarios of cost, efficacy, and failure rate.

Everhart JS, Campbell AB, Abouljoud MM, Kirven JC, Flanigan DC. Cost-efficacy of Knee Cartilage Defect Treatments in the United States. *Am J Sports Med. Jan 2020;48(1):242-251. doi:10.1177/0363546519834557*

VERICEL

Treatment of Chondral Defects of the Knee

Health Technology Assessment
Washington State Health Care Authority

Contributors:

Lead Investigator: Shivani Reddy, MD, MS
Co-Investigators: Leila Kahwati, MD, MPH; Caroline Rains, MPH
Research Assistant: William Tanner, MS
Clinical Advisor: Joseph Marchese, MD
Project Coordinator: Caroline Rains, MPH
Scientific Reviewer: Gerald Gartlehner, MD, MPH
Library/Document Preparation: Mark Howell, MLS

Presented by:

Shivani Reddy, MD, MSc

September 20, 2024
sreddy@rti.org

Overview of Presentation

- Policy context
- Background
- Methods
- Findings
- Conclusions
- Questions

Policy Context

- The State of Washington Health Care Authority chose chondral defect repair of the knee for an HTA because of high concerns of safety and medium concerns for efficacy and high concerns for cost.

- Treatments to include in review include
  - Matrix-induced autologous chondrocyte implantation (MACI)
  - Osteochondral autologous transplantation (OATS) / osteochondral allograft transplantation (OCA)
  - Microfracture

Background

Background: Knee Anatomy and Articular Cartilage

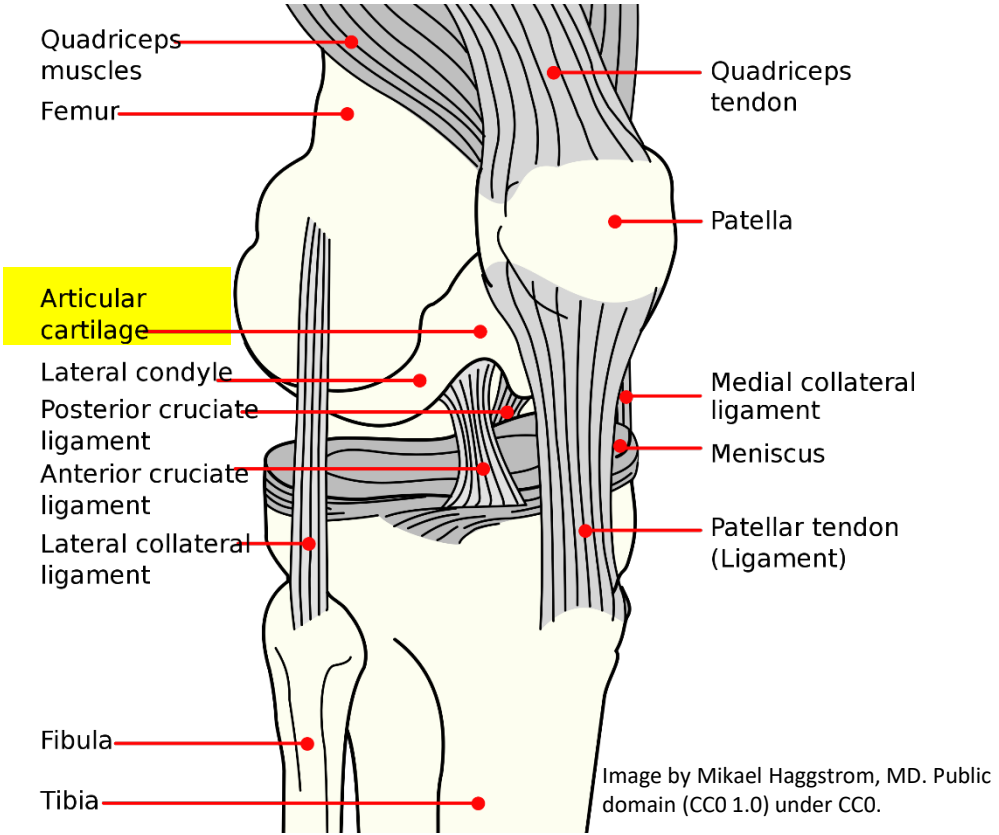
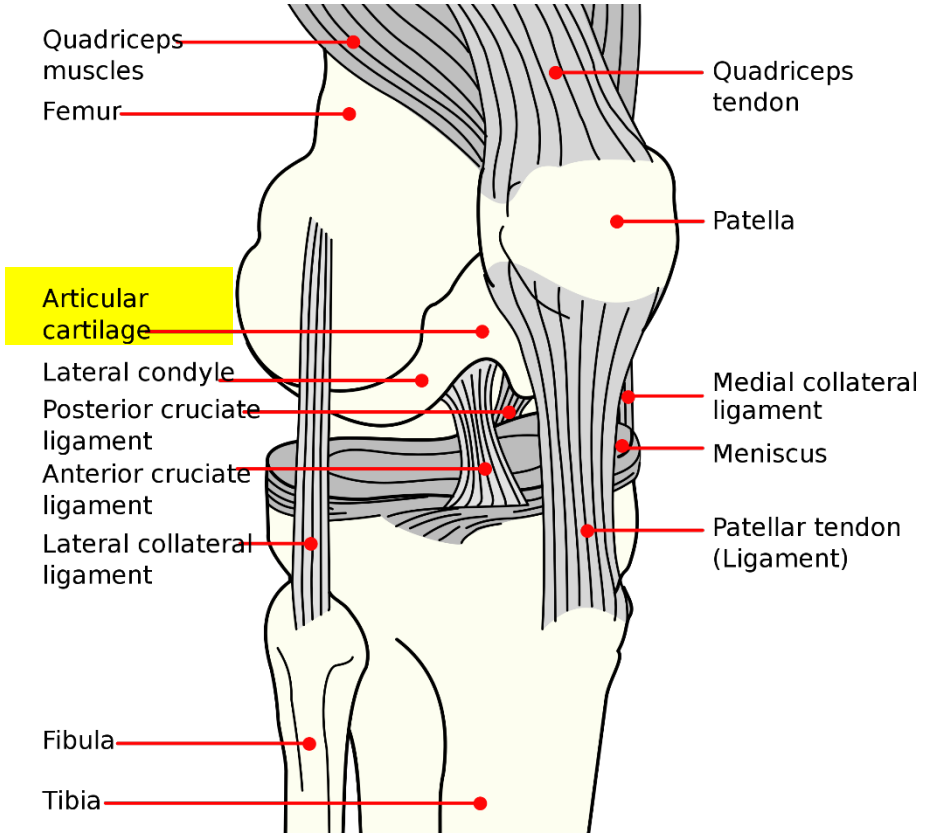


Image by Mikael Haggstrom, MD. Public domain (CC0 1.0) under CC0.

- Lines surface of bones
- > 90% hyaline cartilage (Type II collagen)
- Smooth and lubricated
- Reduces friction as bones glide over each other

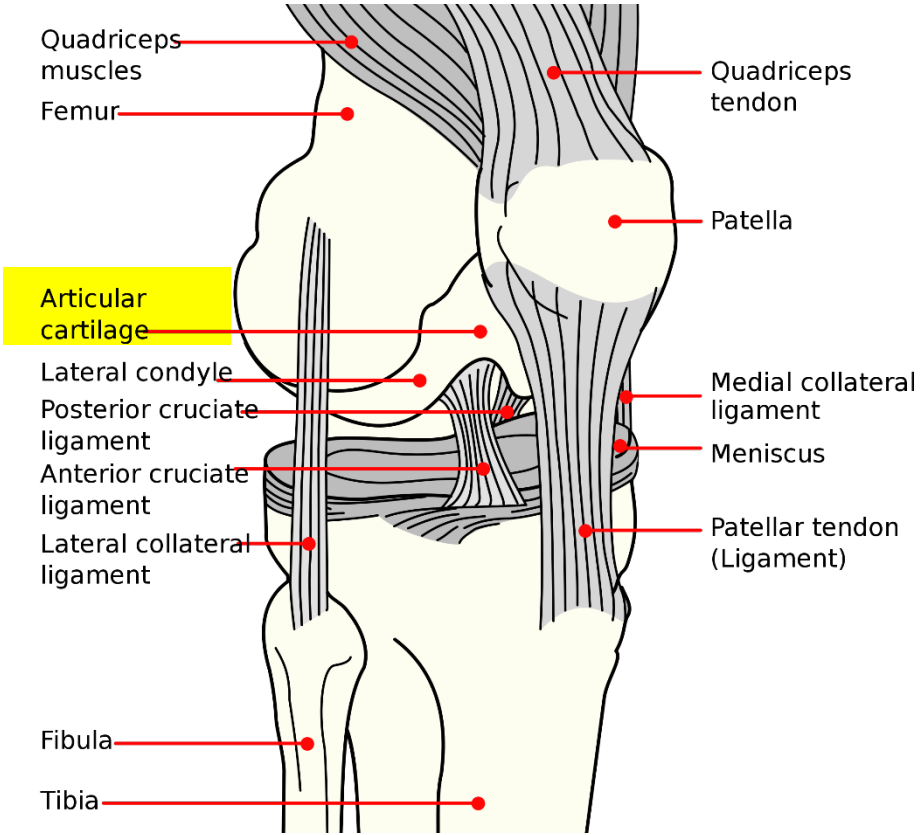
Background: Articular Cartilage Defects



- Poorly vascularized and innervated
- If damaged
  - Limited ability to repair and regenerate hyaline cartilage
  - replaced with fibrocartilage (Type I collagen – more stiff)

Image by Mikael Haggstrom, MD. Public domain (CC0 1.0) under CC0.

Background: Etiology of Articular Cartilage Defects



- Acute trauma
- Anatomical abnormalities
- Developmental defects (osteochondritis dissecans)
- Chronic degeneration

Image by Mikael Haggstrom, MD. Public domain (CC0 1.0) under CC0.

Background: Natural History and Burden of Disease

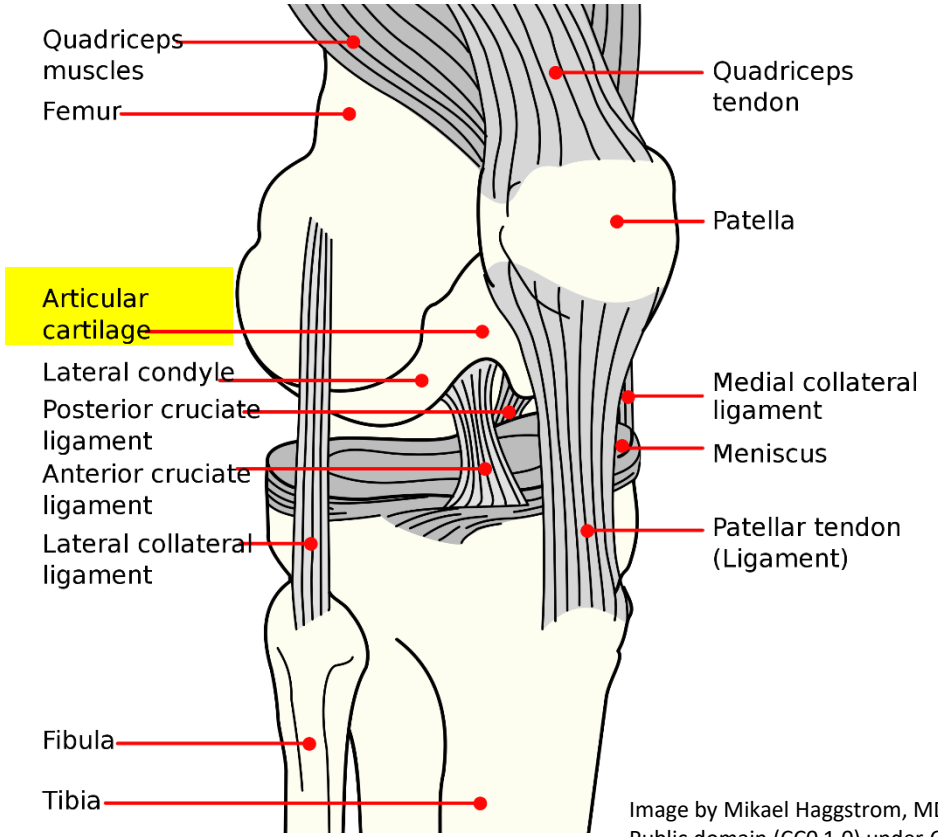


Image by Mikael Haggstrom, MD. Public domain (CC0 1.0) under CC0.

- Increased risk of osteoarthritis
- Symptoms
  - Pain
  - Catching / locking
  - Impaired function
- QOL
  - Similar pain and function to patients awaiting knee replacement

Background: Why Repair Chondral Defects of the Knee?

- If untreated, can lead to limitations in pain, function, QOL and an earlier risk of OA

- Alternative treatment to repairing the cartilage is knee replacement
  - Chondral defect repair is a stop-gap measure to delay knee replacement
  - Knee replacement generally not recommended for patients < 50 years

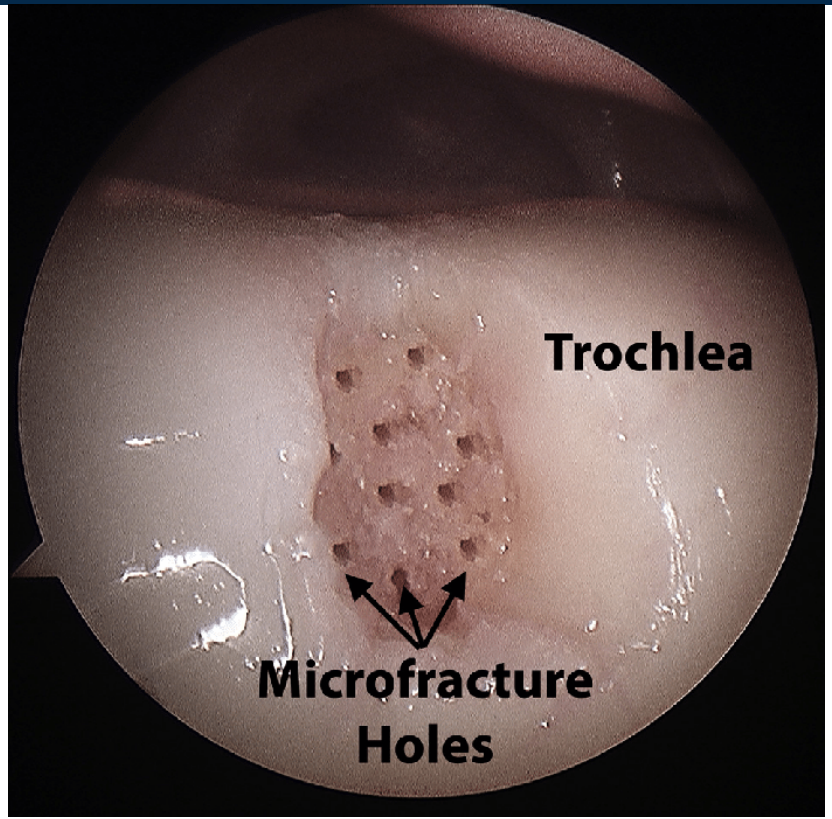
Background: Overview of Treatment

Three categories of treatment

- Bone marrow stimulation techniques
  - Induce a healing response from the body to fill defect with new cartilage
- Osteochondral restoration
  - Transplant articular cartilage tissue into the chondral defect
- Cell-based regeneration
  - Culture patient's cells and transplant

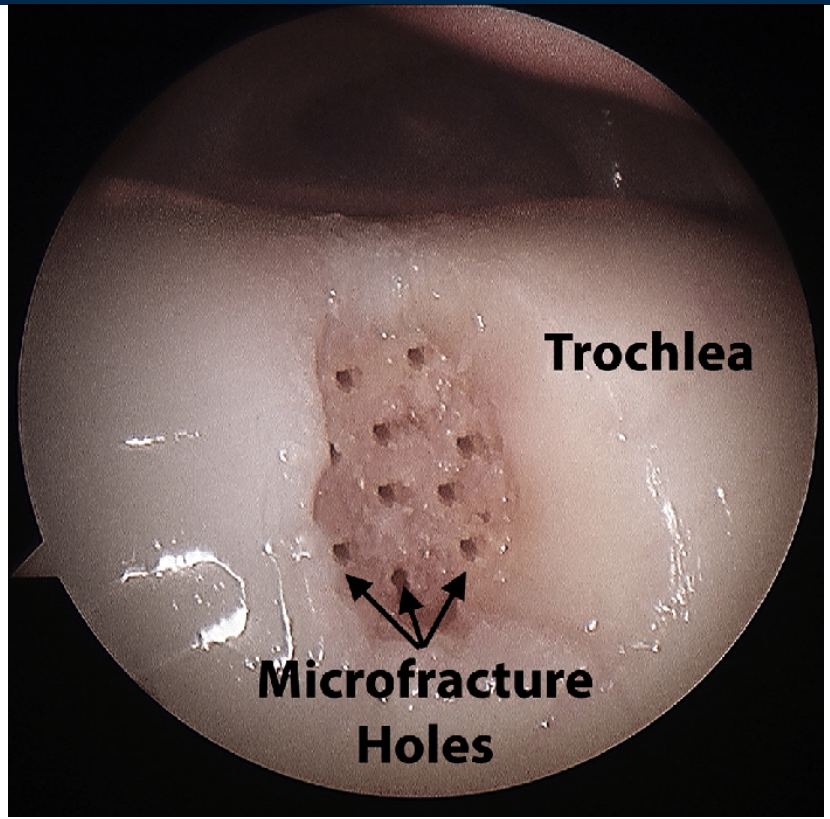
Background: Microfracture

- Bone marrow stimulation technique
- Sharp pick creates channels down to the subchondral bone
  - Allows stem cells from the bone marrow to migrate to the bone surface → new cartilage



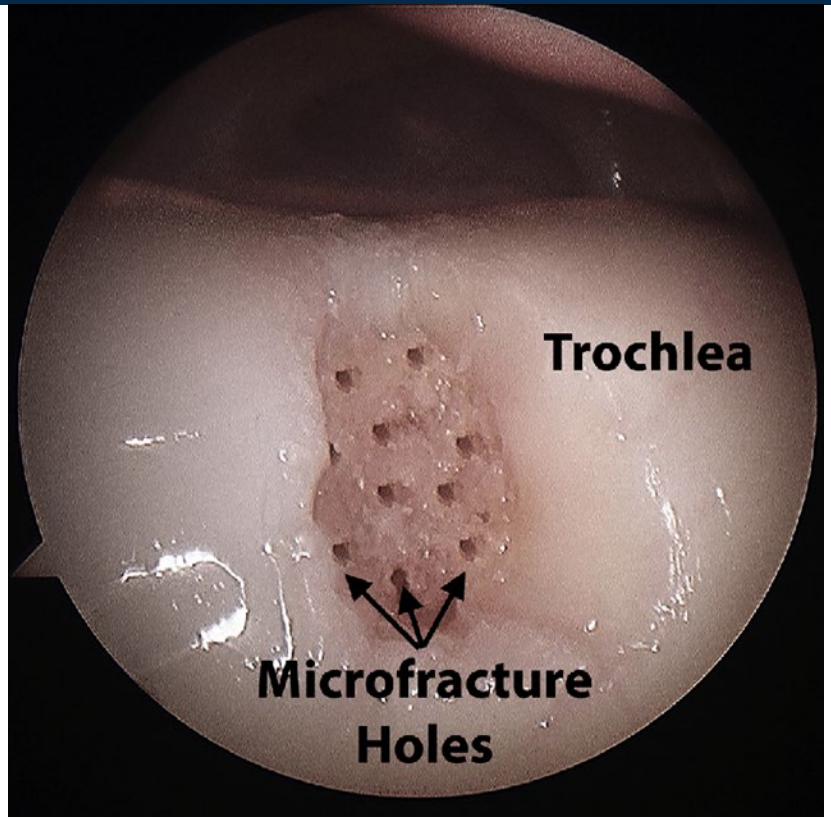
Background: Microfracture

- Small amount of hyaline cartilage
- Large amount of fibrocartilage (stiff, less durable)
- Autologous matrix-induced chondrogenesis (AMIC): MF with collagen membrane covering site to enhance repair



Background: Microfracture

- Most common chondral defect repair procedure in US
- Widely available
- Does not require specialized expertise
- Minimally invasive
- Lower cost

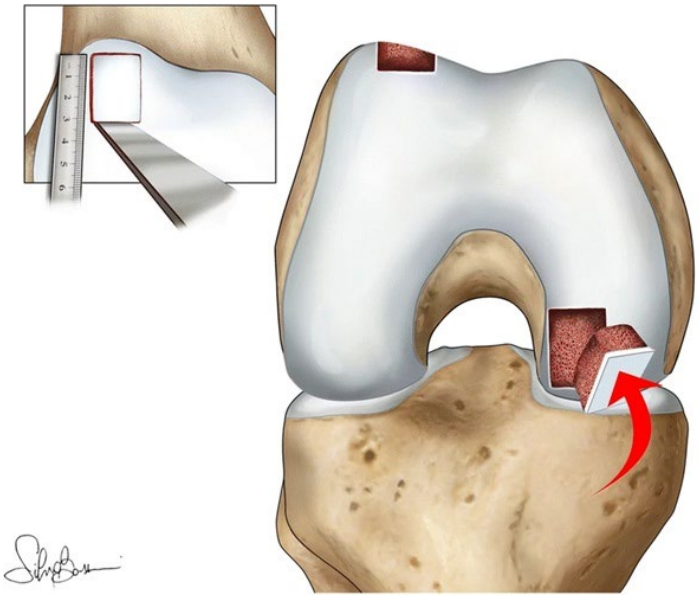


Background: Osteochondral Restoration (OATS and OCA)

Defects including surface cartilage lesions as well as deeper lesions to subchondral bone

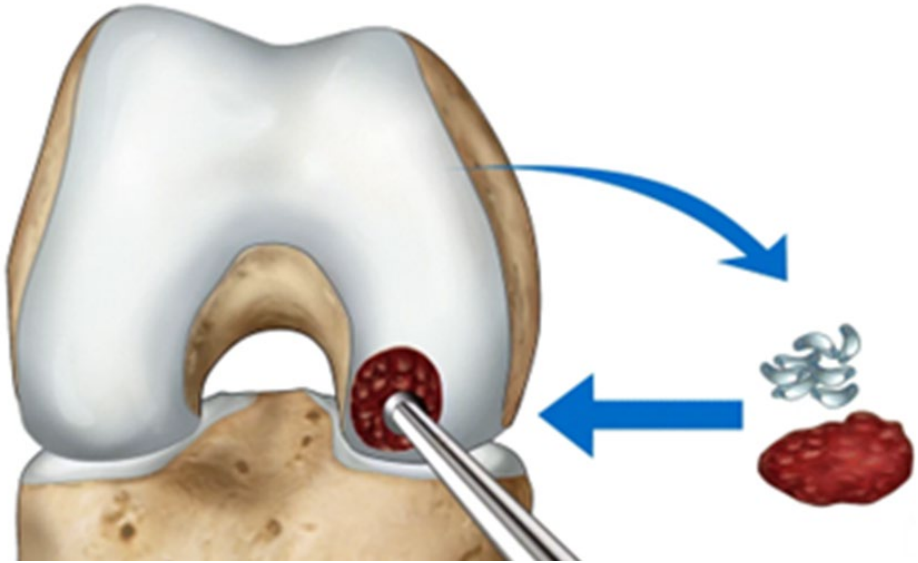
OATS
- Harvest patient's own cartilage
- Transplant into defect
- Limited by size

OCA
- Transplant donor cartilage
- Allows treatment of larger lesions



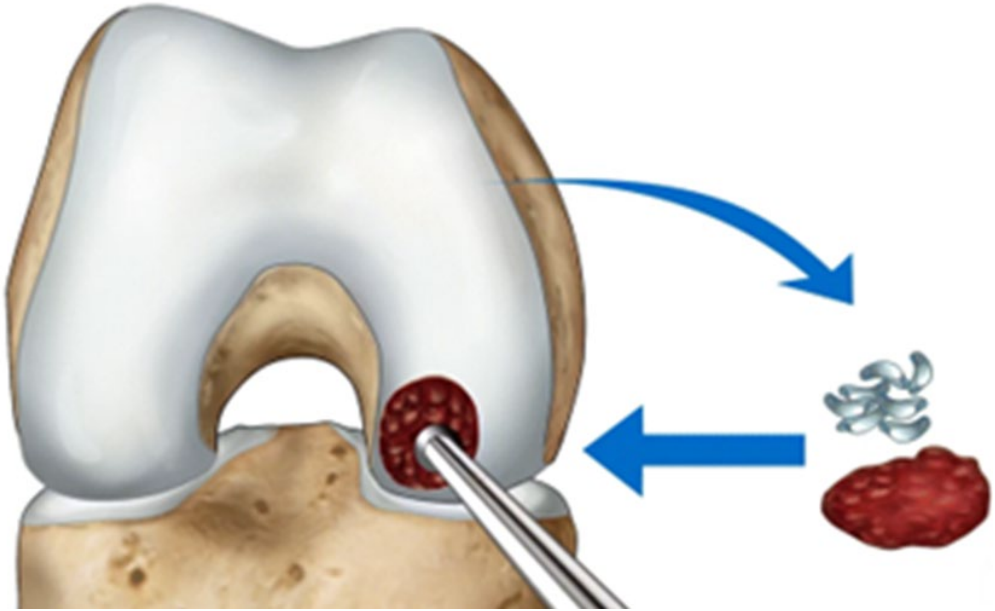
Background: MACI

- Two stages
- Stage 1
  - Harvest chondrocytes from a less-weightbearing part of knee joint
  - Transfer cells onto a scaffold
  - Culture cells 6-8 weeks



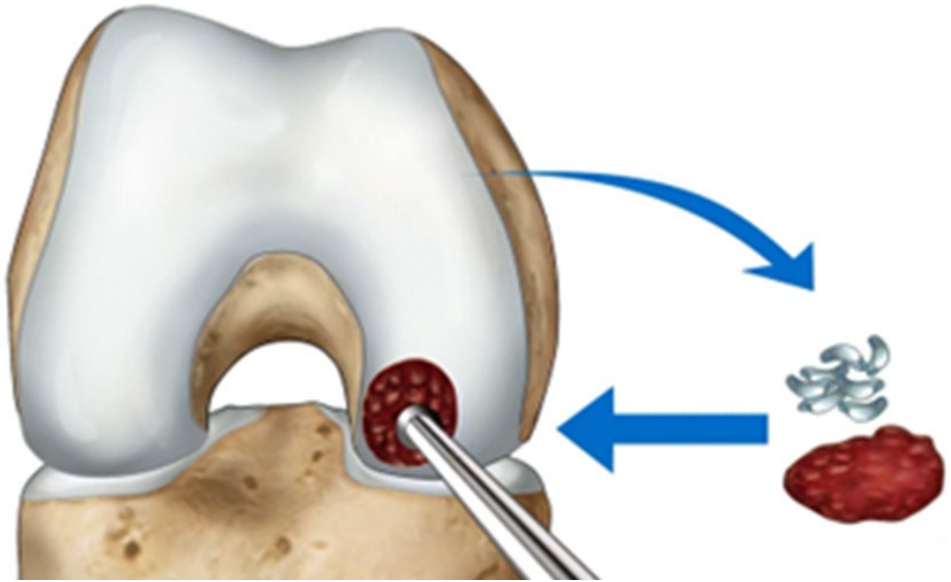
Background: MACI

- Stage 2
  - Implant membrane into chondral defect



Background: MACI

- More durable hyaline cartilage
- Demands more technical skill and resources
- More expensive



Background: Indications for a Procedure

Patient characteristics

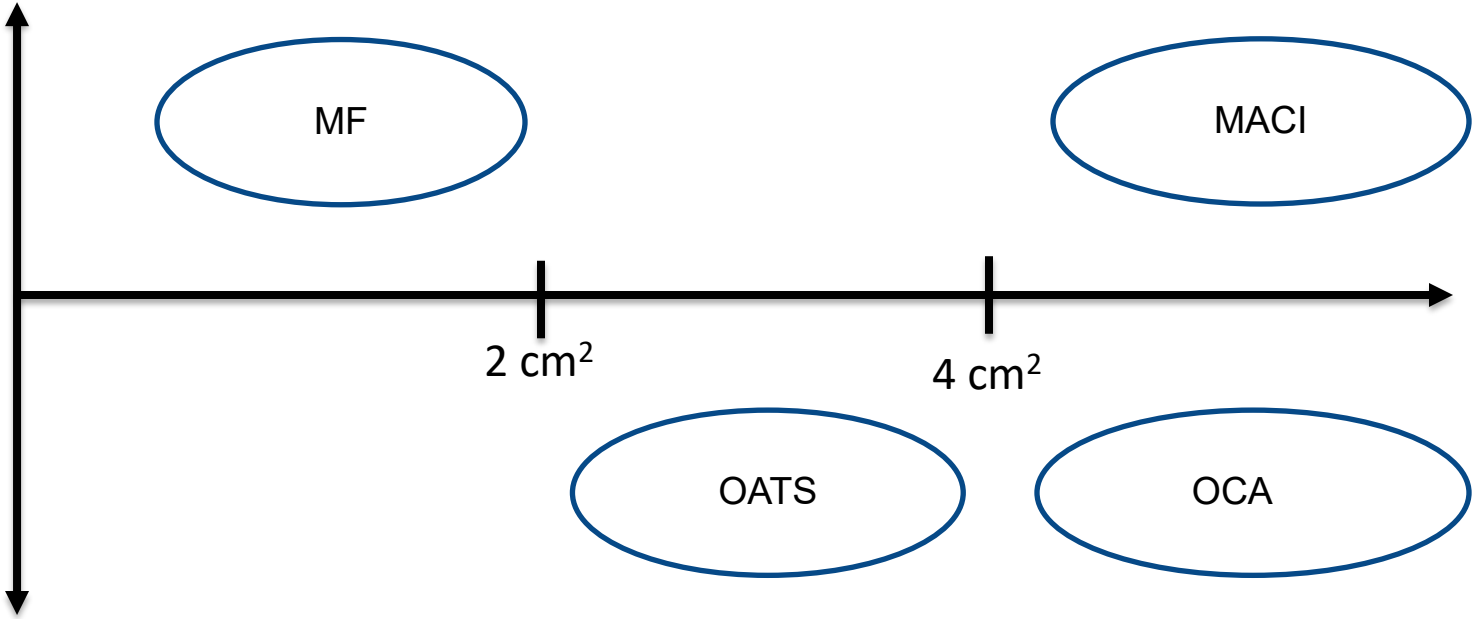
- Age
- Activity level
- Comorbidities (OA)
- Limb alignment

Background: Defect Characteristics

- Size (cm^2)
- Depth (surface lesions or subchondral bone involvement)
- Location of lesion (femoral condyles, trochlea, patella)

Background: Defect Characteristics

Depth: Cartilage only



Depth: Subchondral bone

Background: Regulatory approvals

- No regulatory regulations for surgeries (MF and OATS)
- OCA follows rules of tissue and organ donation
- Products used in articular cartilage repair regulated through the FDA Center for Biologics and Evaluation and Regulation (CBER) through (HTC/P pathway)
  - MACI: porcine or collagen scaffolds (Vericel)
  - OCA: cell-free implant vs. cadaveric donor tissue (Agili-C)
  - MF: collagen scaffold covering surgical site (Chondro-gide)

Clinical Practice Guidelines (CPGs)

No clinical practice guidelines from surgical societies were obtained.

Coverage Policies: State of Washington

- The last review of cartilage repair surgeries in 2011; looked at OATS/OCA only
  - Cover procedures for patients < 50 yo, full thickness cartilage defects
  - Excluded patients with inflammatory arthritis, malignancy, other chronic disease which may cause increased harm to the patient and less benefit.
  - Excluded chondral defects of the ankle
  - No size limits indicated
- No decision on MF
  - Likely due to “standard of care”
- No prior decision on MACI

Methods

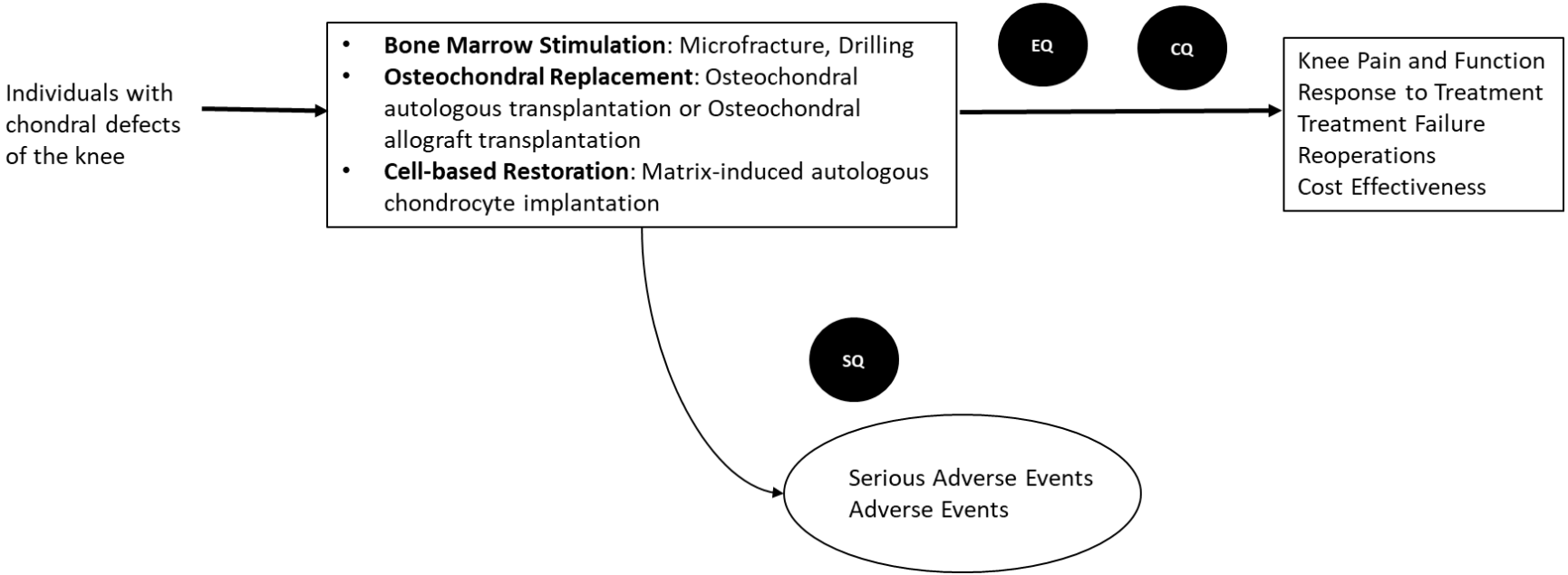
Key Questions

- **Effectiveness Question (EQ 1).** What is the effectiveness of the following treatments for chondral defects of the knee?
  - Bone marrow stimulation procedures (microfracture)
  - Osteochondral restoration: OATS and OCA
  - Cell-based regeneration: MACI

- **Safety Question (SQ 1).** What are the harms associated with treatments for chondral defects of the knee listed above?

- **Cost Question (CQ 1).** What is the cost-effectiveness of treatments for chondral defects of the knee listed above?

Analytic Framework



Abbreviations: CQ = cost question; EQ = efficacy question; HTA = health technology assessment; SQ = safety question

PICOTS

	Include	Exclude
Population	• Individuals with damage to the articular cartilage of the knee—specifically of the femur, tibia, or patella surfaces • Any age (includes those with open or closed growth plates)	• Individuals with an articular cartilage defect in a joint other than the knee • Studies conducted in animals, in vitro, or in silico

PICOTS

	Include	Exclude
Intervention	• Bone marrow stimulation procedures (MF) • OATS / OCA • MACI • Procedures/ products - FDA approved, FDA Breakthrough Device designation, Phase 3 clinical trials • Second-line after a failed first-line (e.g., initial failed bone marrow stimulation procedure; MACI performed second-line)	• 1st and 2nd generation ACI • Experimental treatments or other procedures not listed as included interventions

Abbreviations: ACI = autologous chondrocyte implantation; FDA = U.S. Food and Drug Administration; MACI = matrix-induced autologous chondrocyte implantation; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation

PICOTS

	Include	Exclude
Comparator	Comparators for all procedures • Conservative therapy (e.g., physical therapy, injections, oral analgesics) • Chondroplasty • Knee replacement (total or partial) • Sham surgery Additional comparator for OATS/OCA • MF Additional comparators for MACI • MF • OATS / OCA	• Head-to-head comparisons of the same procedure with different techniques (e.g., MACI with scaffold A vs. MACI with scaffold B, OCA with cadaveric tissue vs. synthetic tissue) with exceptions of first- vs second-line procedures • Waitlist control • No comparator

Abbreviations: MACI = matrix-induced autologous chondrocyte implantation; MF= microfracture; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation

PICOTS

	Include	Exclude
Outcomes	Effectiveness • Knee symptoms and function • Response • Treatment failure • Reoperation • Avoidance of OA, knee replacement Harms • AE • SAE • Specific AE (e.g., infection, bleeding) Cost • Cost-effectiveness, cost-utility	Intermediate outcomes (e.g., imaging outcomes, pathology findings), non-validated measurement tools, non-US cost inputs

Abbreviations: AE = adverse events; OA = osteoartritits; SAE = serious adverse events

PICOTS

	Include	Exclude
Study Design	*EQ and SQ:* RCTs, NRSIs *CQ:* CEA, CUA, or CBA performed from the societal or payer perspective	Editorials, commentaries, narrative reviews, conference abstracts, case reports, case series, case-control studies, other observational study designs without a comparator group; systematic reviews used to identify primary research studies
Setting	Very high development on UN Human Development Index; published in English	Countries other than very high development; published in non-English language

Abbreviations: CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; CQ = cost question; EQ = efficacy question; NRSI = nonrandomized studies of interventions; RCT= randomized controlled trial; SQ = safety question; UN = United Nations

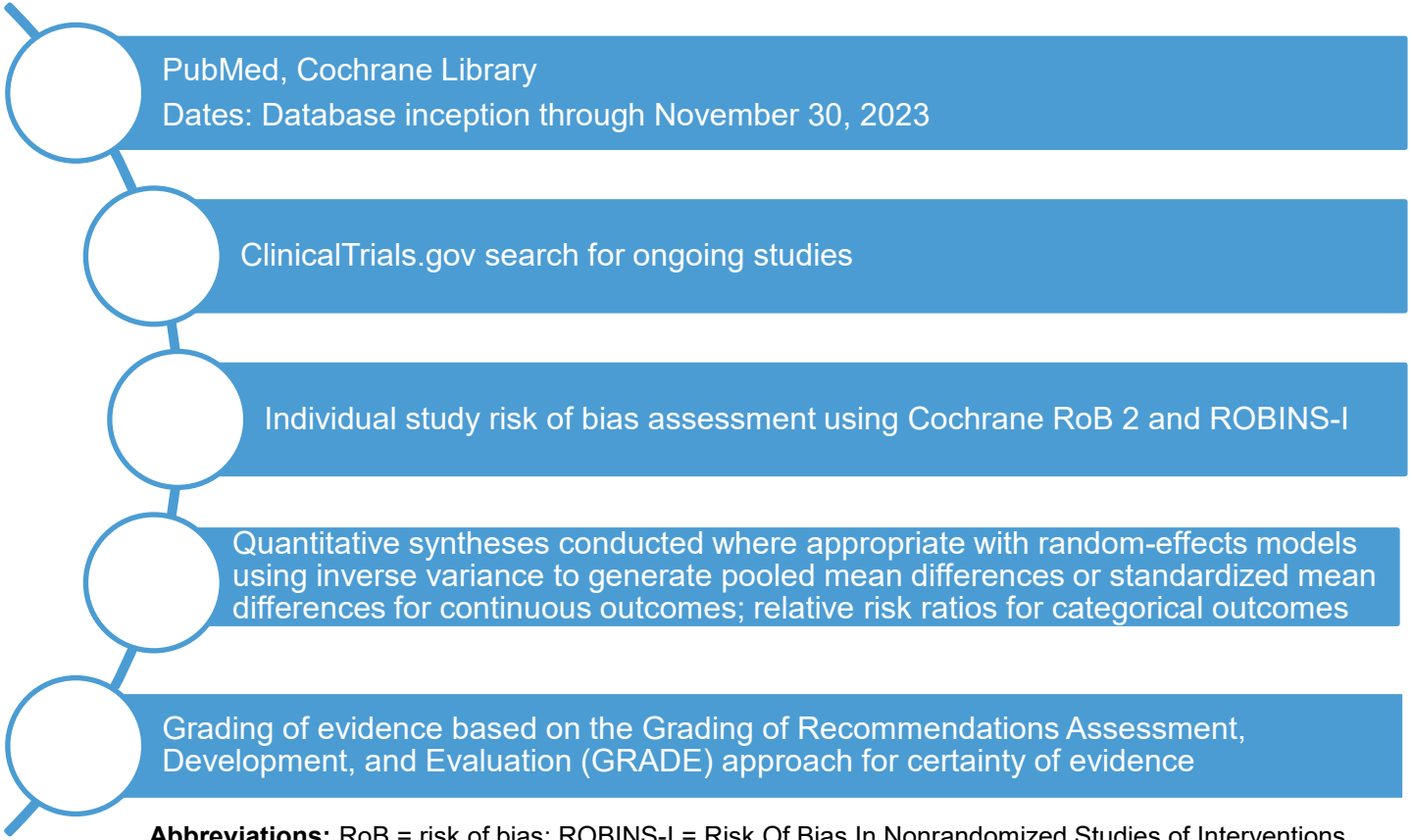
Validated Measures Reported by Included Studies

Outcome Focus: Symptoms and Function

Outcome Focus: Function

Instrument Name	Abbreviation
Cincinnati Knee Rating System	CKRS
Hospital for Special Surgery Knee Rating Scale	HSS
International Knee Documentation Committee Subjective Score	IKDC
Knee Injury and Osteoarthritis Score Subscales	KOOS
Lysholm score	n/a
Tegner Score	n/a

Search and Assessment Methods



Abbreviations: RoB = risk of bias; ROBINS-I = Risk Of Bias In Nonrandomized Studies of Interventions

Certainty of Evidence Grades and Definitions

Outcomes assessed: Patient-reported outcomes, response, treatment failure, reoperation, return to sport or work, adverse events, serious adverse events, cost

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

Summary of Findings

Summary of Search Yield

Comparison	EQ1	SQ1	CQ1
MACI vs Chondroplasty (k=1)	1	0	0
MACI vs MF (k=5)	5	4	0
MACI vs OATS (k=2)	2	0	0
OCA vs OATS (k=2)	2	0	0
OATS vs Chondroplasty (k=1)	1	0	0
OATS vs MF (k=8)	7	3	1
Cell-free Implants vs MF/Chondroplasty (k=1)	1	1	0
AMIC vs MF (k=1)	1	1	0
1st Line vs 2nd Line Procedures (k=4)	4	0	0

Abbreviations: AMIC = autologous matrix-induced chondrogenesis; k= MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation

Topline Summary

- MACI may more effective than MF (moderate to low COE)
- OATS is possibly effective than or of comparable effectiveness as MF with low COE
- First-line MACI or OCA may be more effective than performing these procedures as second-line procedures with low COE
- Harms for all comparisons are probably comparable but few events in many studies or not reported (low to very low COE)

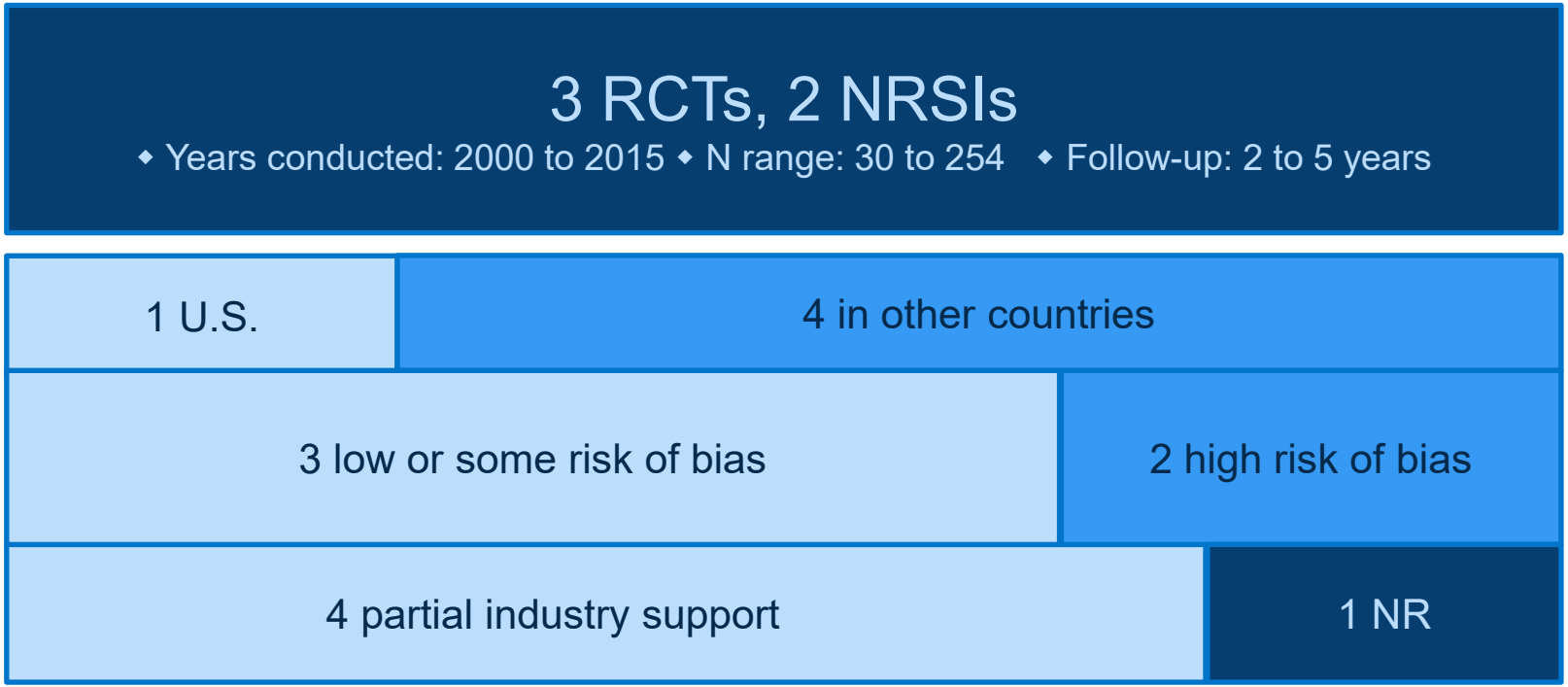
Population: Age

- Most studies had inclusion criteria ages 18 to 50
- 1 study exclusively performed in patients < 18 years
- Inclusion criteria for 7 studies included both adolescents and adults
- Mean ages ranges from 14 to 53 years

Page in Report: 16-50, Tables 6, 8, 10, 12, 14, 16, 20, 22, 24, C-1, C-5, C-10, C-14, C-18, C-22, C-27, C-32, C-37

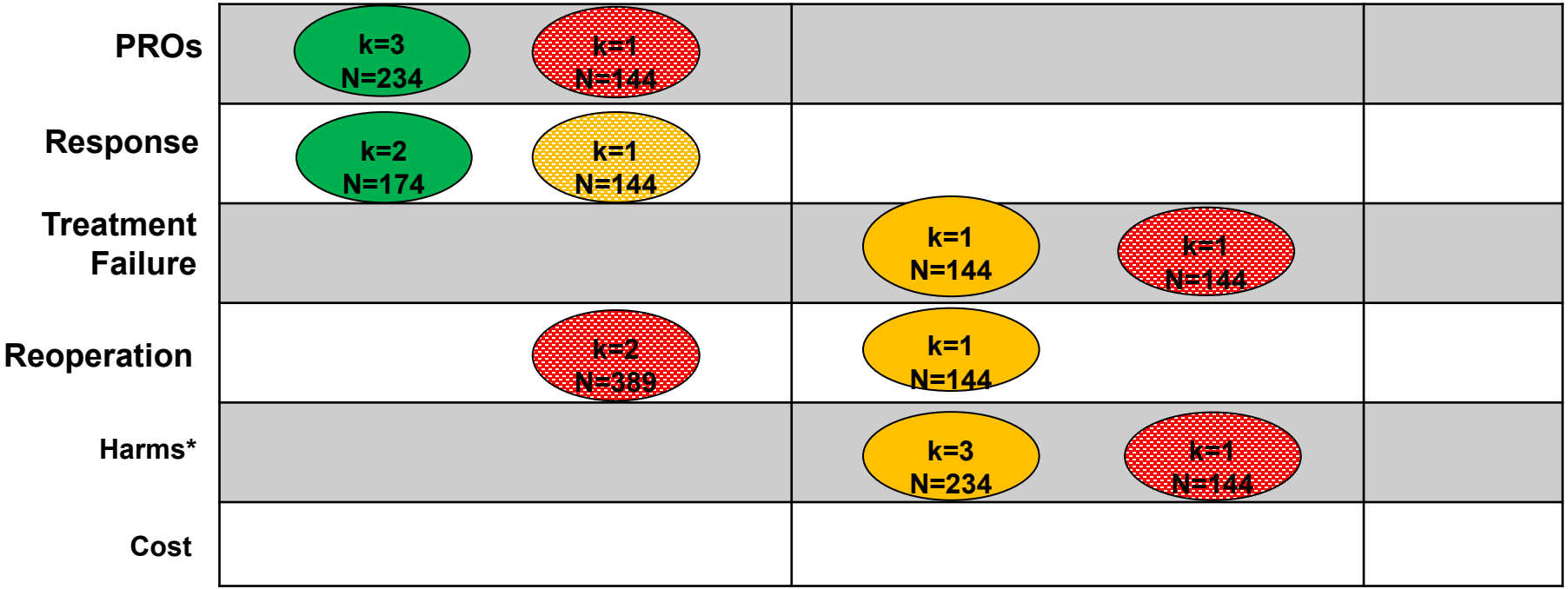
Findings: MACI vs MF

Study Characteristics: MACI vs MF



Abbreviations: MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; N = number of participants; NR = not reported; NRSI = nonrandomized studies of interventions; RCT = randomized controlled trial

Evidence Map: MACI vs MF



Legend

GRADE Certainty of Evidence (COE)

Very Low | Low | Moderate | High

Solid – RCTS
Speckled - NRSIs

K = number of studies; N = total number of participants; NRSI = nonrandomized studies of interventions; PROs = patient-reported outcomes; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; RCT = randomized controlled trial

* AEs and SAEs combine and assigned lowest COE

MACI vs MF: Effectiveness

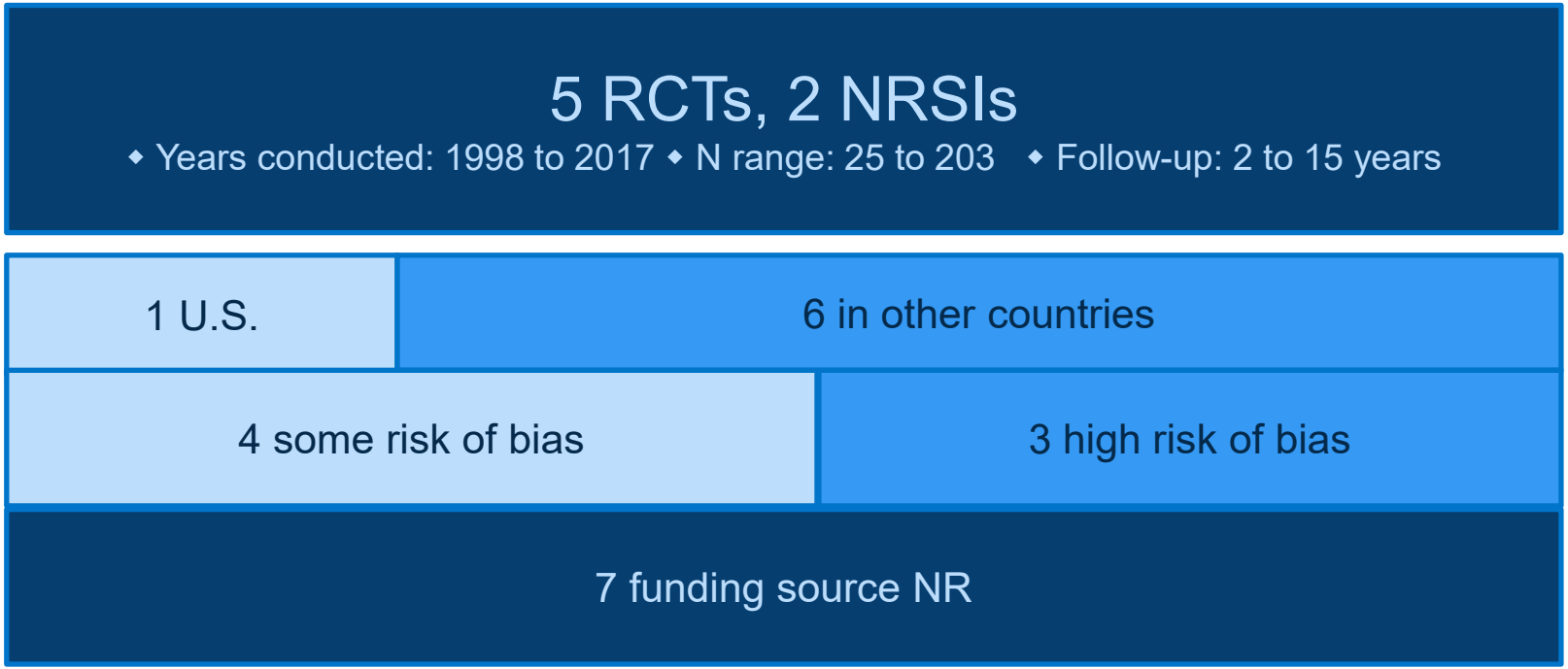
- PROs
  - Greater effectiveness of MACI for both RCTs and NRSIs
  - Results for most outcomes across studies were clinically significant
- Response
  - Greater response of MACI to treatment for both RCTs and NRSIs
  - Range RR 1.3 to 3.4
- Treatment Failure
  - Treatment failure was comparable both RCTs and NRSIs
- Reoperations
  - Comparable reoperations for MACI and MF (RCTs)
  - Greater effectiveness of MACI (NRSIs)

MACI vs MF: Harms

- Any Adverse Events (AE)
  - Comparable harms for both RCTs and NRSIs
- Any Serious Adverse Events (SAE)
  - Only RCTs reported any SAEs: comparable
- Very few harms outcomes for most studies
- Most common specific AE reported: knee pain, knee swelling
- Reported SAEs: septic arthritis, DVT (1 of each)

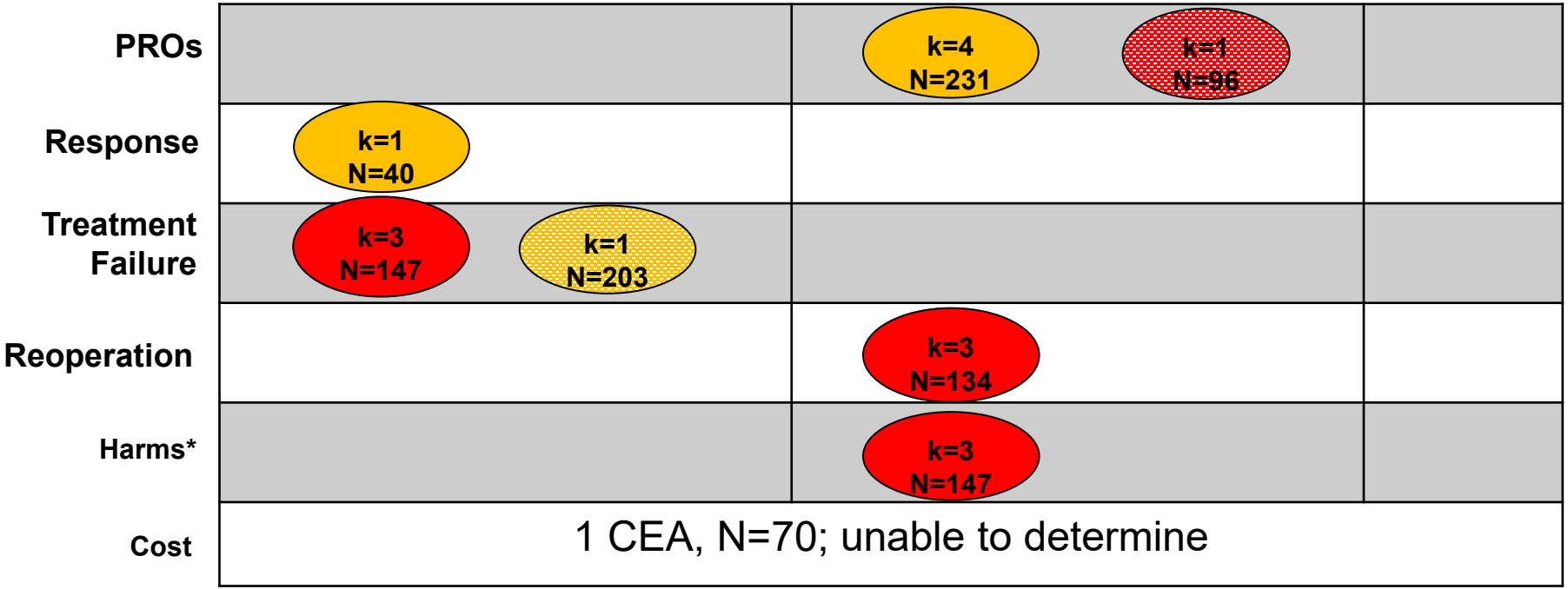
Findings: OATS vs MF

Study Characteristics: OATS vs MF



Abbreviations: N = number of participants; NR = not reported; NRSI = nonrandomized studies of interventions; RCT = randomized controlled trial

Evidence Map: OATS vs MF



Legend

GRADE Certainty of Evidence

Very Low | Low | Moderate | High

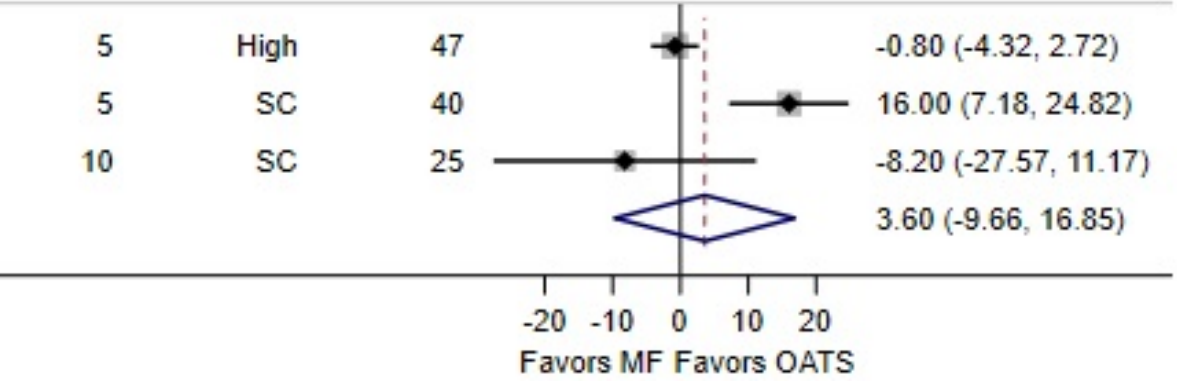
Solid – RCTs
Speckled - NRSIs

CEA = cost effectiveness analysis; K = number of studies; N = total number of participants; NRSI = nonrandomized studies of interventions; MF = microfracture; OATS = osteochondral autologous transplantation; RCT = randomized controlled trial
* AEs and SAEs combine and assigned lowest COE

OATS vs MF: Effectiveness

PROs: OATS and MF groups reported similar improvements in PROs

Author, Year	Mean age years (range)	Mean defect size cm (range)	Follow-up Time (years)	Risk of Bias	Sample Size	Mean difference (95% CI)
Lim, 2012	30 - 33	2.7 - 2.8	5	High	47	-0.80 (-4.32, 2.72)
Solheim, 2018	31 - 35	3.4 - 3.5	5	SC	40	16.00 (7.18, 24.82)
Ulstein, 2014	32 - 33	2.6 - 3.0	10	SC	25	-8.20 (-27.57, 11.17)
Overall, DL (I^2 = 84.6%, p = 0.002)						3.60 (-9.66, 16.85)



Abbreviations: CI = confidence interval, DL= DerSimonian & Laird estimator for pooling estimates, MF=microfracture, OATS = osteochondral autologous transplantation; SC = some concerns.

OATS vs MF: Effectiveness

- Response
  - One small RCT (N=40) reported greater response to treatment for OATS
- Treatment Failure
  - Similar for both groups for 3 RCTs
  - Favored OATS for fewer treatment failures in 1 NRSI
- Reoperations
  - Similar for both groups for 3 RCTs

OATS vs MF: Harms

- Any Adverse Events
  - Harms were similar for each procedure
  - Among the 3 studies reporting any adverse events, 2 reported few events
  - The third study reported individual adverse events including knee pain, joint swelling, and crepitation that were higher in the MF group

- Serious Adverse Events
  - No studies reported any serious adverse events

OATS vs MF: Subgroups

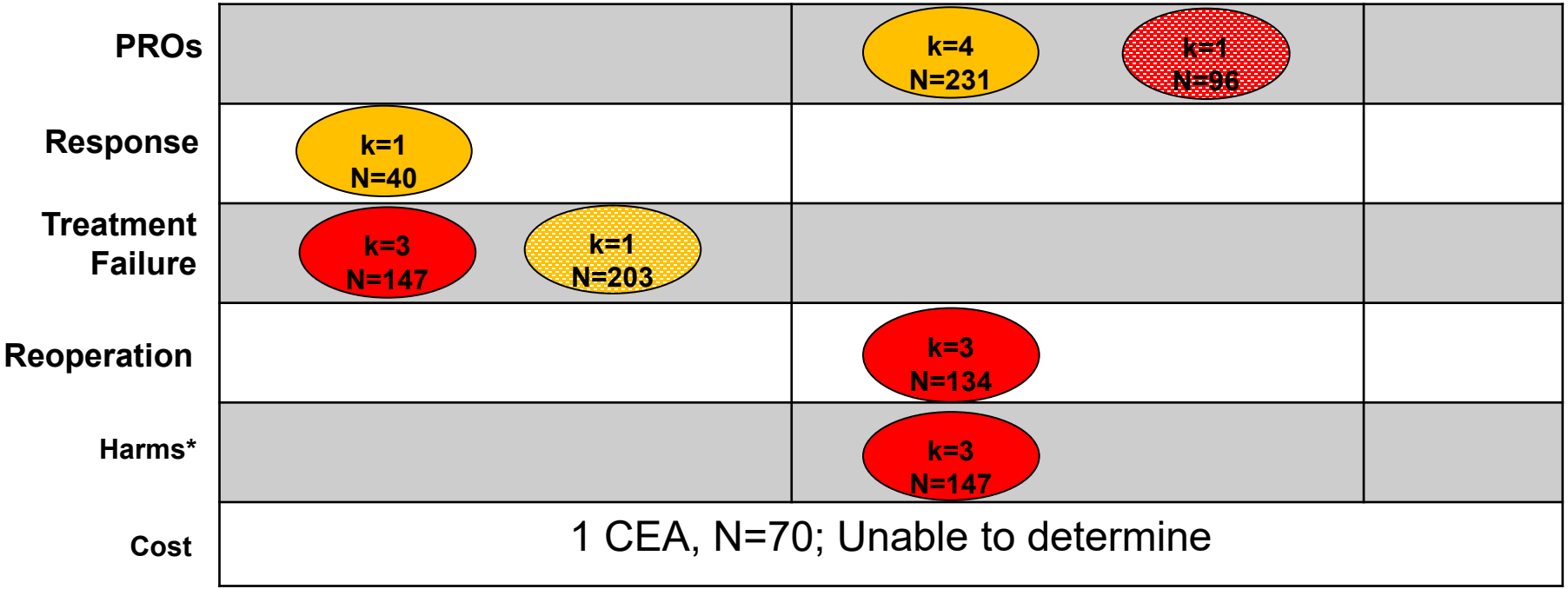
- RCTs:
  - Two studies reported greater effectiveness for smaller lesion size in the MF group

- NRSIs
  - One study reported improved results in the OATS group compared to the MF group for age younger than 51 and lesion size less than 5 cm^2

OATS vs MF: Cost-effectiveness

- One study based on U.S. data reported cost-effectiveness outcomes
- The study reported mixed results on whether OATS or MF was more cost-effective depending on which PRO used for effectiveness measure
  - MF lower cost per point improvement using Lysholm and HSS scores
  - OATS lower cost per point improvement using Tegner score
  - OATS more cost-effective using return to sport

Evidence Map: OATS vs MF



Legend

GRADE Certainty of Evidence

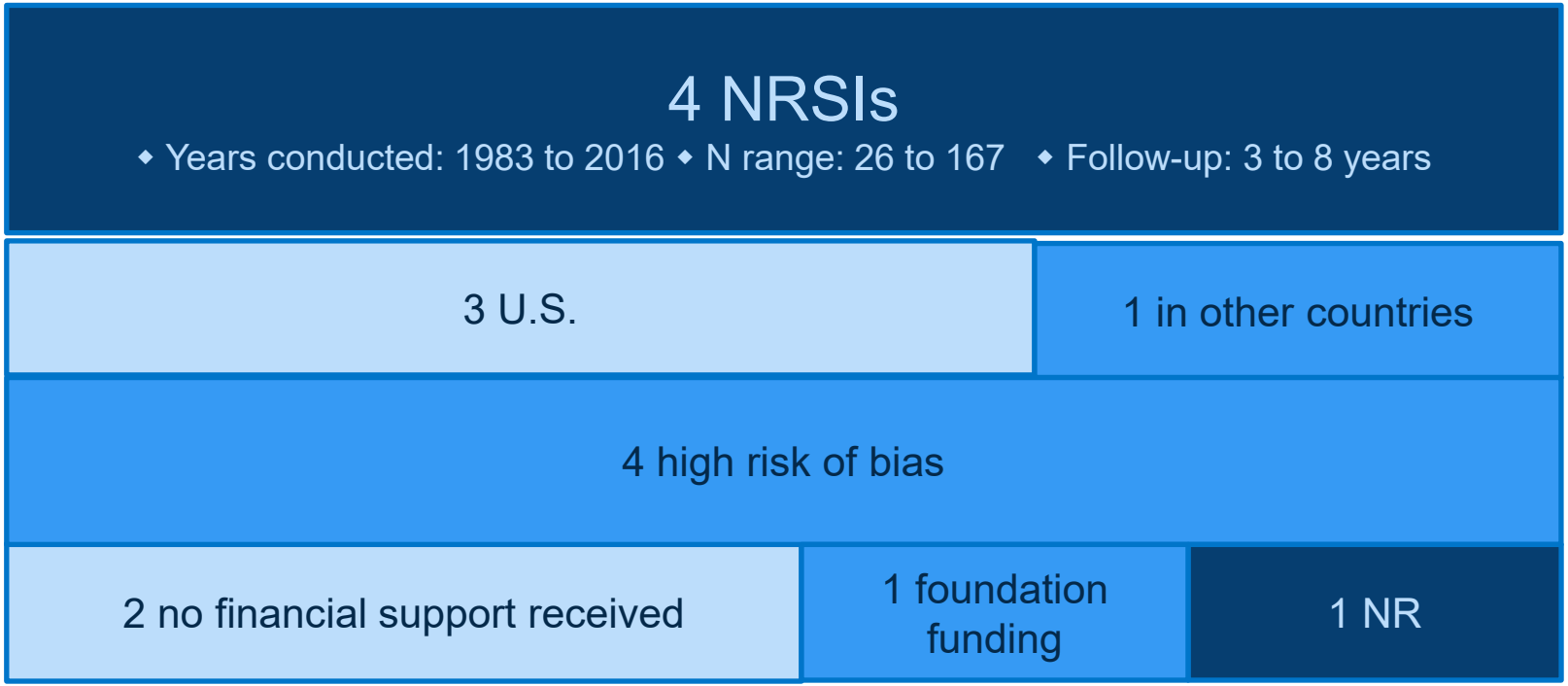
Very Low | Low | Moderate | High

Solid – RCTs
Speckled - NRSIs

CEA = cost effectiveness analysis; K = number of studies; N = total number of participants; NRSI = nonrandomized studies of interventions; MF = microfracture; OATS = osteochondral autologous transplantation; RCT = randomized controlled trial
* AEs and SAEs combine and assigned lowest COE

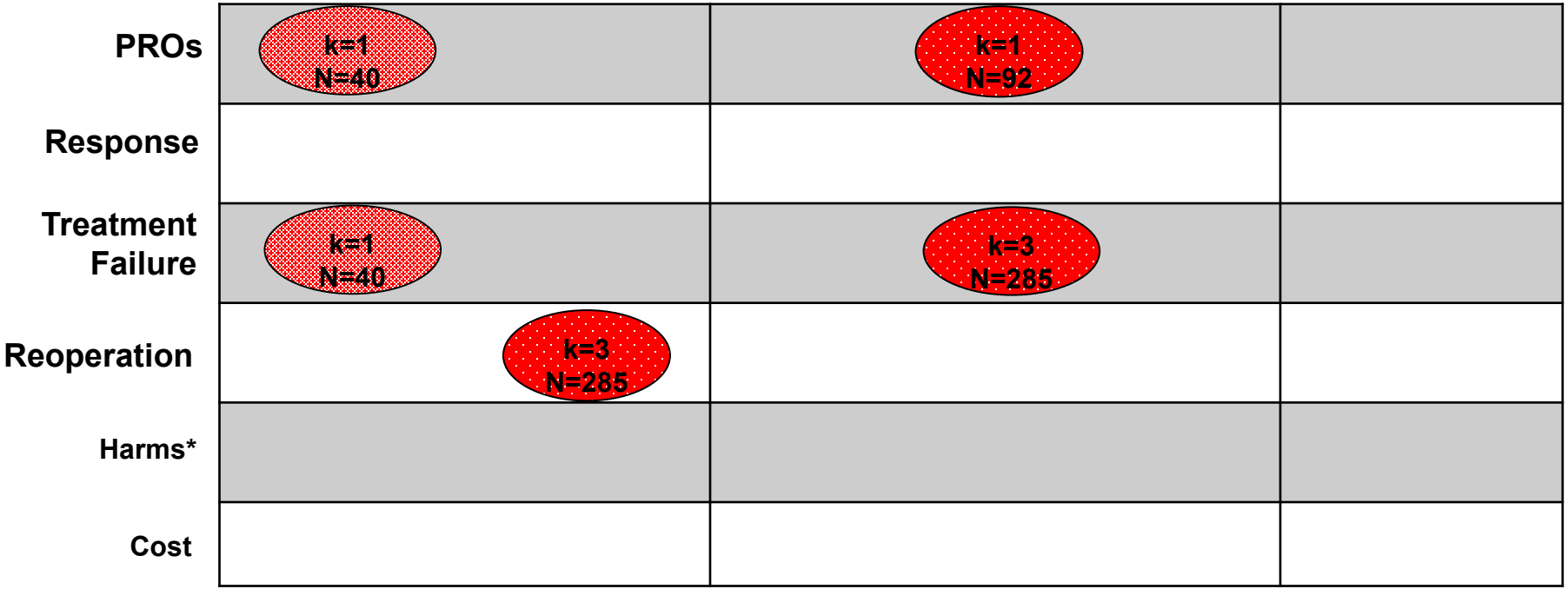
Findings: 1st-line vs 2nd-line Procedures

Study Characteristics: 1st line vs 2nd line



Abbreviations: N = number of participants; NR = not reported; NRSI = nonrandomized studies of interventions; RCT = randomized controlled trial

Evidence Map: 1st line vs 2nd line



Legend

GRADE Certainty of Evidence

Very Low | Low | Moderate | High

Checkered – MACI
Pattern - OCA

K = number of studies; N = total number of participants; MACI = matrix-induced autologous chondrocyte implantation; OCA = osteochondral allograft transplantation
* AEs and SAEs combine and assigned lowest COE

1st line vs 2nd line procedures: Effectiveness and Harms

- Fewer treatment failures for first-line compared to second-line MACI and OCA procedures
- First-line MACI procedures reported greater improvement in PROs compared to second-line MACI procedures.
- PRO results for first-line and second-line OCA were similar
- No harms were reported.

Comparisons with Limited Evidence

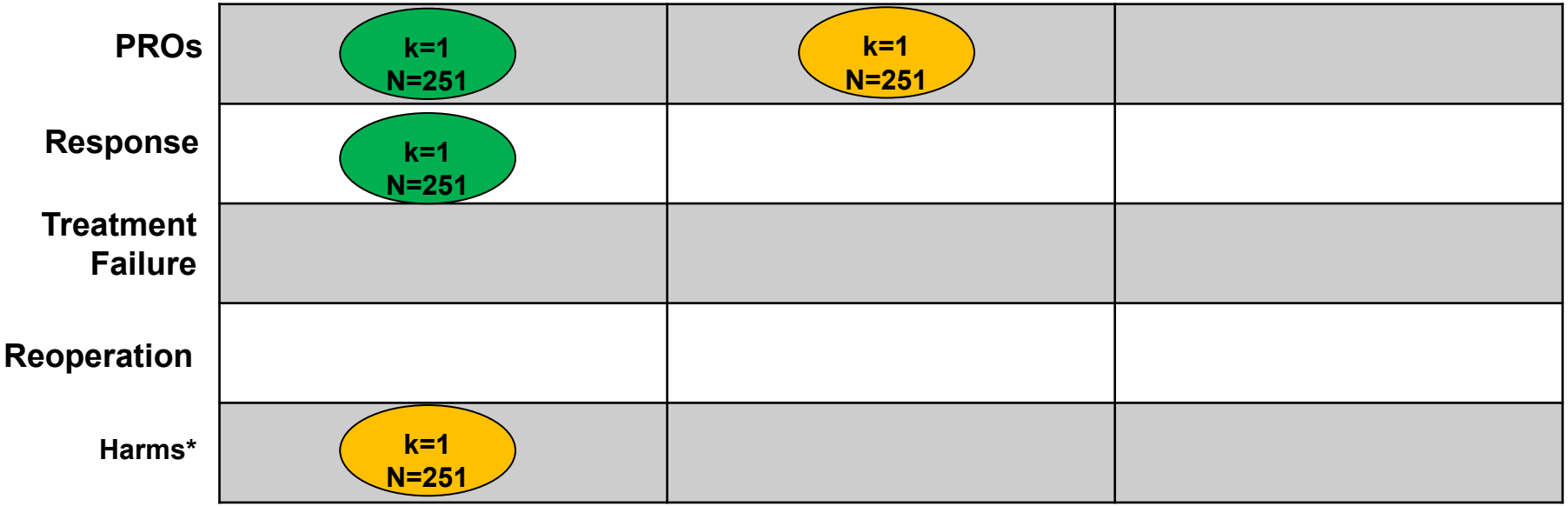
Other comparisons

- MACI vs OATS (n=2)
- MACI vs OCA (n=0)
- OCA vs OATS (n=2)

Newer procedures

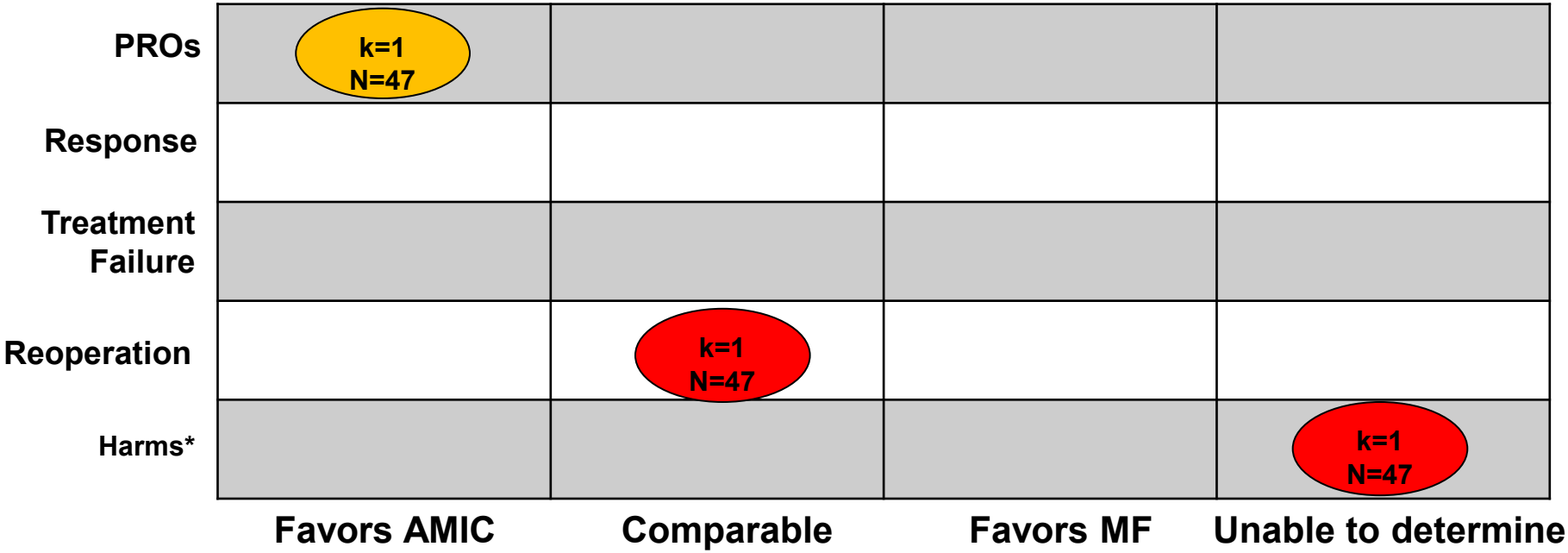
- Cell-free implants vs MF/Chondroplasty (n=1)
- AMIC vs MF (n=1)

Comparisons with Limited Evidence: Cell-free implants vs. MF/Chondroplasty



CEA = cost effectiveness analysis; K = number of studies; N = total number of participants; NRSI = nonrandomized studies of interventions; MF = microfracture; OATS = osteochondral autologous transplantation; RCT = randomized controlled trial
* AEs and SAEs combine and assigned lowest COE

Evidence Map: AMIC vs MF



Legend

GRADE Certainty of Evidence

Very Low | Low | Moderate | High

Solid – RCTs
Speckled - NRSIs

CEA = cost effectiveness analysis; K = number of studies; N = total number of participants; NRSI = nonrandomized studies of interventions; MF = microfracture; OATS = osteochondral autologous transplantation; RCT = randomized controlled trial
* AEs and SAEs combine and assigned lowest COE

Discussion

Discussion: Limitations of Comparative Effectiveness Research

- Head-to-head trials not set up to study each procedure under its optimal condition
- Few studies performed subgroup analyses

Discussion: Limitations of Comparative Effectiveness Research

- Comparative effectiveness evidence provides some information about which procedures have greater or comparative effectiveness

- But in the absence of data on important considerations, surgeons and patients need to tailor decisions to the clinical context as we do with most evidence-based medicine and recommendations.

Discussion: Limitations of Comparative Effectiveness Research

- Example: patient has larger defect, cannot afford longer rehabilitation time
  - Surgeon may opt for MF even though evidence of benefit stronger for MACI

- Example: defect involves subchondral bone, would lean towards OATs or OCA rather than MACI or MF

Discussion: Comparisons with Limited Evidence

- Chondral defect repair vs knee replacement (k=0)
  - Knee replacement reserved for older patients
  - More expensive

- Chondral defect repair vs conservative therapy (k=0)

Limitations of the Evidence

- Many RCTs and NRSIs with high ROB
- Only 1 study reported time to return to work or rehabilitation time
- A variety of PROs reported – difficult to assess across studies
- Heterogeneity of definition for response, treatment failure, and reoperations
- Range of reported follow-up times

Limitations of the HTA

- Included only validated measures for disease specific PROs; did not include general QOL outcomes
- Did not include first- or second-generation ACI procedures
  - First-generation procedures phased out
  - Second-generation procedures no FDA products in the US
- Included only comparative study designs
  - Increases ability to infer causal inference

Payor Coverage Policies

Discussion: Payor Coverage Policies

Procedure	Medicare National Coverage Determination	Cigna	Kaiser Permanente	Premera Blue Cross	Regence BlueShield	United Health
MF	—	—	—	—	—	✓
OATS / OCA	—	✓	—	✓	—	✓
ACI / MACI	—	✓	—	✓	✓	✓

Notes: ✓ = covered; X = not covered
Abbreviations: ACI = autologous chondrocyte implantation; MACI = matrix-induced autologous chondrocyte implantation; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation

Discussion: Payor Coverage Policies

Company	Procedures Covered	Growth Plate Requirements	Lesion Requirements	Other Requirements
Cigna	OATS, OCA, ACI/MACI	Closed growth plates required	NR	NR
Premera Blue Cross	OATS, OCA, ACI/MACI	Closed growth plates required	OATS: Focal, full-thickness lesions 1.0 to 2.5 cm^2 OCA; ACI/MACI: Focal, full-thickness lesions >1.5 cm^2	Too young for TKA (e.g., ≤ 55 years)
Regence BlueShield	ACI/MACI	Closed growth plates required	Focal, full-thickness lesions >1.5 cm^2	Too young for TKA (e.g., ≤ 55 years); BMI < 35
United Health	MF, OATS, OCA, ACI/MACI	Closed growth plates required	MF: Full- and partial-thickness lesions ≤ 4 cm^2; ACI/MACI: Full-thickness lesions ≥ 2 cm^2 ;OATS/OCA: NR	≤ 55 years (ACI/MACI)

Abbreviations: ACI = autologous chondrocyte implantation; BMI = body mass index; MACI = matrix-induced autologous chondrocyte implantation; NR = not reported; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation; TKA = total knee arthroplasty

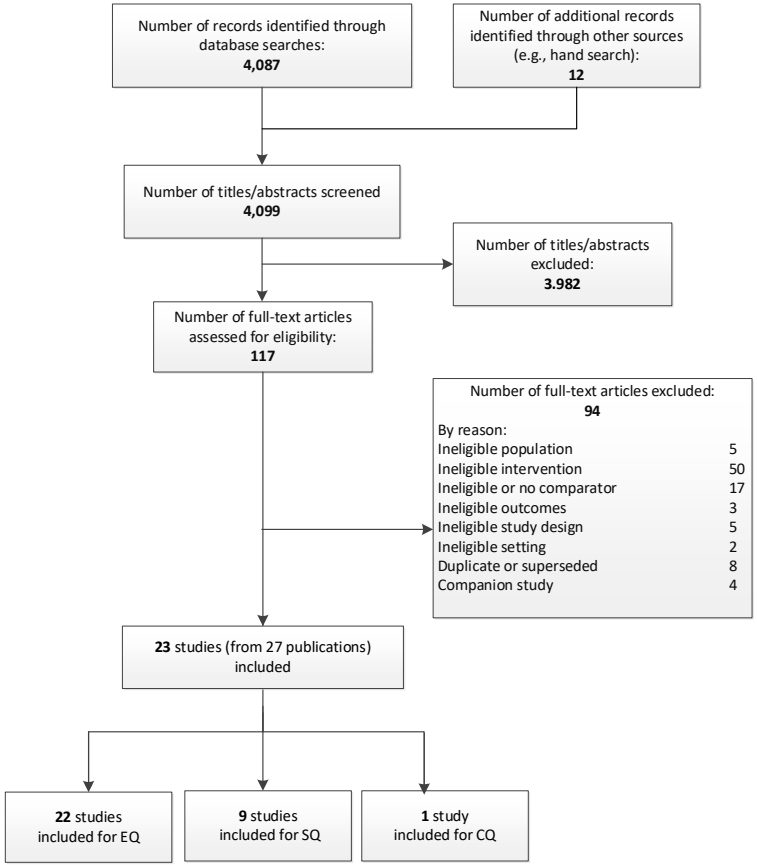
Topline Summary

- MACI may more effective than MF (moderate to low COE)
- OATS is possibly effective than or of comparable effectiveness as MF with low COE
- First-line MACI or OCA may be more effective than performing these procedures as second-line procedures with low COE
- Harms for all comparisons are probably comparable but few events in many studies or not reported (low to very low COE)

Questions?

Additional Slides

Summary of Search Yield



Findings: Other Comparisons

Study Characteristics for Other Comparisons

2 RCTs, 4 NRSIs

- Years conducted: 1998 to 2019
- N range: 18 to 2,598
- Follow-up: 1 to 10 years

2 U.S.	4 in other countries

6 high risk of bias

2 industry support	4 sponsor NR

1 MACI vs Chondroplasty vs OATS	1 MACI vs OATS	2 OCA vs OATS	1 cell-free implant vs MF/ chondroplasty	1 AMIC vs MF

Abbreviations: AMIC = autologous matrix-induced chondrogenesis; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; N = number of participants; NR = not reported; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation; NRSI = nonrandomized studies of interventions; RCT = randomized controlled trial

Other Comparisons: Effectiveness

Patient-reported Outcomes

No. Studies (No. Participants) Procedures Follow-up	Summary of Effect	Overall COE/ Direction
1 NRSI (N=18) MACI vs OATS Follow-up: 3.5 years	Outcomes of Lysholm, CKRS, and Tegner scores were higher in the MACI group compared to OATS group.	Very low for greater effectiveness of MACI
1 RCT (N=251) Cell-free implant vs MF/chondroplasty Follow-up: 6 to 24 months	PROs include KOOS total and subdomains of pain, ADLs, and QOL. Follow-up total KOOS scores increased from baseline to 6 and 24 months, greater in the cell-free implant group compared to MF (MD, 22.5 [95% CI, 17.0 to 28.0], P<0001 at all timepoints). Individual KOOS domains have similar results, but authors did not report specific values.	Moderate for greater effectiveness of cell-free implant
1 RCT (N=47) AMIC vs MF Follow-up: 1 to 5 years	CKRS: 1-year follow-up results show within-group improvement across all groups (82 vs. 67, P<0.001 for AMIC and MF, respectively); 5-year follow-up results favor sutured and glued AMIC over MF, though values were not reported.	Low for greater effectiveness of AMIC

Other Comparisons: Effectiveness

Return to Sport or Work

No. Studies (No. Participants) Procedures Follow-up	Summary of Effect	Overall COE/ Direction
1 NRSI (N=47) MACI vs chondroplasty Follow-up: 1 year	Similar percentage of individuals resumed normal sport and work activities, 1 year post-surgery for MACI and chondroplasty groups (71% vs. 60%, respectively; Calculated RR 1.2 (95% CI, 0.70 to 2.0))	Very low for comparative effectiveness
1 NRSI (N=22) MACI vs OATS Follow-up: 1 year	Smaller percentage of individuals resumed normal sport and work activities, 1 year post surgery for MACI compared to OATS groups (71% vs. 100%, respectively)	Very low for greater effectiveness of OATS
1 NRSI (N=47) OATS vs chondroplasty Follow-up: 1 year	Greater percentage of individuals resumed normal sport and work activities, 1 year post-surgery for OATS compared to chondroplasty group (100% vs. 60%, respectively; calculated RR 1.6; 95% CI, 1.2 to 2.1)	Low for greater effectiveness of OATS

Other Comparisons: Effectiveness

Response

No. Studies (No. Participants) Procedures Follow-up	Summary of Effect	Overall COE/ Direction
1 RCT (N=251) Cell-free implant vs MF/chondroplasty Follow-up: 24 months	Response, defined by an overall increase in KOOS score greater than 30, was significantly greater in the cell-free implant group, compared to MF. Calculated ARD 43.7% (95% CI, 31.7 to 55.7)	Moderate for greater effectiveness of cell-free implant

Treatment Failure

No. Studies (No. Participants) Procedures Follow-up	Summary of Effect	Overall COE/ Direction
1 RCT (N=251) Cell-free implant vs MF/chondroplasty Follow-up: 24 months	Treatment failure, defined as any secondary procedure (surgical or injection) to the joint, was similar in both groups. (ARD -3.5%, 95% CI, -12.4% to 5.5%)	Moderate for comparable effect

Other Comparisons: Effectiveness

Reoperation

No. Studies (No. Participants) Procedures Follow-up	Summary of Effect	Overall COE/ Direction
2 NRSI (N=3,330) OCA vs OATS Follow-up: NR or 10 years	For any reoperation performed, similar rate of reoperation in both studies; 17% in the OCA group and 22% in the OATS group (P=0.08) for 1 study and 24% vs. 22% for the other study.	Low for comparable effectiveness
1 RCT (N=47) AMIC vs MF Follow-up: 1 year	After 1 year, 1 patient treated with glued AMIC received a joint replacement, and 1 patient with MF received an ACI procedure.	Very low for comparable effectiveness

Other Comparisons: Harms

No. Studies (No. Participants) Procedures Follow-up	Summary of Effect	Overall COE/ Direction
Any adverse events		
1 RCT (N=251) Cell free implant vs MF/chondroplasty Follow-up: 24 months	Smaller proportion of individuals experiencing at least 1 AE in the cell-free implant group compared to MF. Calculated ARD -17.8% (95% CI, -29.5 to -6.0)	Moderate for lower harms of cell-free implant
Adverse events		
1 RCT (N=47) AMIC vs MF Follow-up: 5 years	A small number of adverse events were reported for the total study sample, no information by group.	Very low for comparable harms
Any severe adverse events		
1 RCT (N=251) Cell free implant vs MF/chondroplasty Follow-up: 24 months	Few events reported in either group.	Low for comparable harms

HTCC Coverage and Reimbursement Determination
Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.

Based on Legislative mandate: RCW 70.14.100(2).

The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

3. *Factors for Consideration - Importance*

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical committee findings and decisions

Efficacy considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next step: Cover or no cover

If not covered, or covered unconditionally, the chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next step: Cover with conditions

If covered with conditions, the committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.
2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the

task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical committee evidence votes

First voting question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Discussion document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety outcomes	Importance of outcome	Safety evidence/ confidence in evidence
Infection		
Joint swelling/effusion		
Knee joint crepitation		
Pain		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
Lysholm score		
Knee osteoarthritic outcome score (KOOS)		

Cost outcomes	Importance of outcome	Cost evidence
Cost		
Cost-effectiveness		

Special population / Considerations outcomes	Importance of outcome	Special populations/ Considerations evidence
Age		
Sex		
Comorbidity		
Adolescents		
Pregnant individuals		

For safety:

Is there sufficient evidence that the technology is safe for the indications considered?

No relevant studies	Low Risk Safe	Moderate Risk	High Risk Unsafe
	Confidence: Low Medium High	Confidence: Low Medium High	Confidence: Low Medium High

For efficacy/ effectiveness:

Is there sufficient evidence that the technology has a meaningful impact on patients and patient care compared to the evidence-based alternative(s)?

No relevant studies	Less Less effective	Equivocal	More More effective at least in some
	Confidence: Low Medium High	Confidence: Low Medium High	Confidence: Low Medium High

For cost outcomes/ cost-effectiveness:

Is there an accepted scale for cost effectiveness for treatments for this disease? If so, how does this treatment compare with evidence-based alternatives?

No relevant studies	Less Less cost effective	Equivocal	More

			More cost effective at least in some
	Confidence: Low Medium High	Confidence: Low Medium High	Confidence: Low Medium High

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is *insufficient* to make a conclusion about whether the health technology is *safe, efficacious, and cost-effective*;
- Evidence is *sufficient* to conclude that the health technology is *unsafe, ineffectual, or not cost-effective*
- Evidence is *sufficient* to conclude that the health technology is *safe, efficacious, and cost-effective for all indicated conditions*;
- Evidence is *sufficient* to conclude that the health technology is *safe, efficacious, and cost-effective for some conditions or in some situations*

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is:

Not covered	Covered unconditionally	Covered with conditions

Discussion item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Medicare Coverage

[see page ES-15 of final report]

There were no identified Medicare national or local coverage determinations for chondral defect restoration procedures.

Clinical Practice Guidelines

[see page 58 of final report]

Title and Organization	Year	Procedure	AGREE Rating	Summary of Treatment Recommendation(s)
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**[a][57]	2018	Articular cartilage lesions	4	Clinicians may use early progressive knee motion following knee meniscal and articular cartilage surgery. (C) Physicians may need to delay return to activity depending on the type of articular cartilage surgery. (E) Clinicians should use a stepwise progression of weight-bearing to reach full bearing by 6 to 8 weeks after MACI for articular cartilage lesions. (B) Clinicians should provide supervised, progressive, range-of-motion exercises; progressive strength training of the knee and hip muscles; and neuromuscular training to patients with knee meniscus tears and articular cartilage lesions and after meniscus or articular cartilage surgery. (B)
Consensus Guidelines on Interventional Therapies for Knee Pain (STEP Guidelines) from the **American Society of Pain and Neuroscience**[b][59]	2022	Marrow stimulation (ACI) Mosaicplasty (OATS)	4	• Marrow stimulation is an effective treatment for younger patients with small, isolated hyaline defects. (C) • ACI is an effective treatment for young patients with small, isolated cartilage lesions less than 2 cm^2 who have tried and failed conservative care. (C) • Mosaicplasty is an effective long-term treatment option for patients 18 to 50 years old with hyaline cartilage lesions 2 cm^2 to 5 cm^2. (A) OATS is an effective knee joint preservation technique. (C)
Mosaicplasty for symptomatic articular cartilage defects of the knee: **National Institute for Health and Care Excellence (NICE)**[58]	2018	Mosaicplasty (OATS)	4	Current evidence on the safety and efficacy of mosaicplasty for knee cartilage defects is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent, and audit. The procedure should only be done by surgeons experienced in cartilage surgery and who have specific training in mosaicplasty for knee cartilage defects. Clinicians should enter data from all patients having the procedure onto the International Cartilage Regeneration and Joint Preservation Society Patient Registry.

Notes: [a] Recommended grade definitions for the American Physical Therapy Association are as follows: B – Moderate Evidence: single, high-quality randomized controlled trial or a preponderance of level II studies (e.g., prospective studies, trials with high risk of bias) support the recommendation; C – Weak Evidence: single level II study or a preponderance of level III and IV studies (e.g., case-control studies, case series), including statements of consensus by content experts, support the recommendation); E – Expert Opinion (best practices based on the clinical experience of the guidelines development team).

[b] Recommended grades for American Society of Pain and Neuroscience are as follows: Grade A – Extremely recommendable based on at least one randomized controlled trial (good evidence that the measure is effective and that benefits outweigh the harms); C – Neither recommendable nor in advisable based on cohort or case studies and well-designed controls (at least moderate evidence that the measure is effective, but benefits are similar to harms and a general recommendation cannot be justified).

Abbreviations: ACI = autologous chondrocyte implantation; MACI = matrix-induced autologous chondrocyte implantation; OATS = osteochondral autologous transplantation.

Next step: proposed findings and decision and public comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?
2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next step: final determination

Following review of the proposed findings and decision document and public comments:

Final vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no or unclear (i.e., tie), outcome chair will lead discussion to determine next steps.

Washington State Health Care Authority

Final Key Questions and Background

Treatments for Patients with Chondral Defects of the Knee

Background

Chondral defects refer to damage of the surface cartilage lining the bones where they connect, or articular cartilage. Chondral defects can cause pain, reduce function, and may decrease quality of life as much as severe osteoarthritis.[1] Articular cartilage has a limited ability to regenerate and over time is associated with scarring, progressive cartilage degeneration, and increased risk for osteoarthritis.[2,3] One treatment for chondral defects is debridement of damaged cartilage tissue, although this treatment does not replace the cartilage. Chondral restoration procedures aim to replace damaged tissue with healthier cartilage.

This health technology assessment (HTA) reviews the efficacy, safety, and cost-effectiveness of selected chondral defect restoration procedures of the knee, including microfracture, drilling, osteochondral autologous transplantation (OATS), osteochondral allograft transplantation (OCA), and matrix-induced autologous chondrocyte implantation (MACI).

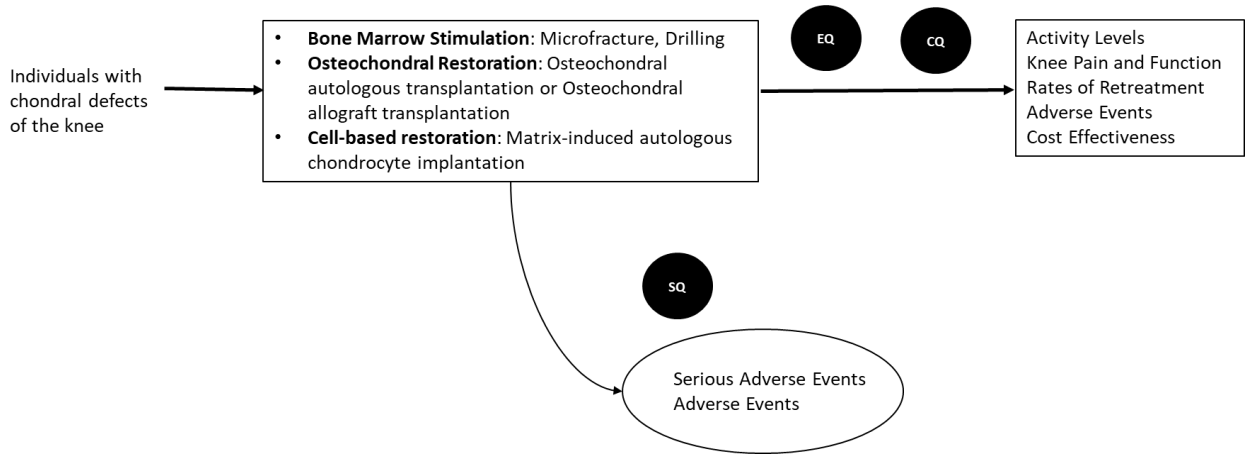
Policy Context

The State of Washington Health Care Authority selected treatment of chondral defects of the knee for a HTA because of medium concerns of efficacy and high concerns for safety and cost.

Scope of this HTA

The analytic framework (***Figure 1***), research questions, and key study selection criteria (***Table 1***) are listed in this section.

Figure 1. Analytic Framework Depicting Scope of This Health Technology Assessment



Abbreviations: CQ = cost question; EQ = efficacy question; SQ = safety question

Washington State Health Care Authority

Research Questions

Efficacy Question. What is the efficacy of the following cartilage restoration treatments for chondral defects of the knee?

- Bone marrow stimulation procedures
  - Microfracture
  - Drilling
- Osteochondral restoration
  - Osteochondral autologous transplantation (OATS)
  - Osteochondral allograft transplantation (OCA)
- Cell-based restoration
  - Matrix-induced autologous chondrocyte implantation (MACI)

Safety Question. What are the harms associated with treatments for chondral defects of the knee listed above?

Cost Question. What is the cost-effectiveness of cartilage restoration treatments for chondral defects of the knee listed above?

Study Selection Criteria

Table 1 provides the study selection criteria we will use to include studies in the HTA and are organized by population, intervention, comparator, outcomes, timing, setting, and study design (PICOTS) criteria.

Table 1. Proposed Population, Intervention, Comparator, Outcome, Timing, and Setting (PICOTS) for Health Technology Assessment

PICOTS	Include	Exclude
Population	• Individuals with a focal defect of the articular cartilage of the knee—specifically of the femur, tibia, or patella • Any age	• Individuals receiving a restorative procedure for a chondral defect in a joint other than the knee • Studies conducted in animals, *in vitro*, or *in silico*
Intervention	• Microfracture surgery (including drilling) • Osteochondral autologous transplantation (OATS) • Osteochondral allograft transplantation (OCA) • Matrix-induced autologous chondrocyte implantation (MACI; 3rd-generation ACI) Interventions that use biologic or synthetic materials will be included if the materials are FDA-approved or there is evidence that they are in advanced commercial development for the US (e.g. Phase 3 trials; FDA-designation as a Regenerative Medicine Advanced Therapy (RMAT), Fast Track, or	• Other treatments not specifically listed as included • Procedures using materials that are not in advanced commercial developmentAutologous chondrocyte implantation (1st and 2nd generation ACI)

Washington State Health Care Authority

PICOTS	Include	Exclude
	Breakthrough Therapy candidate (e.g.Prochondrix CR [AlloSource], Novocart 3D® [Aesculap Biologics])	
Comparator	For Microfracture: • Chondroplasty • Knee replacement (total or partial) • Sham surgery • Non-surgical interventions or conservative therapy (e.g., physical therapy, injections, oral analgesics) For OATS, OCA: • Microfracture or drilling • MACI • Chondroplasty • Knee replacement (total or partial) • Sham surgery • Non-surgical interventions or conservative therapy (e.g., physical therapy, injections, oral analgesics) For MACI: • Microfracture or drilling • OATS • OCA • Chondroplasty • Knee replacement (total or partial) • Sham surgery • Non-surgical interventions or conservative therapy (e.g., physical therapy, injections, oral analgesics)	• Head-to-head comparisons of the same procedure with different techniques (e.g., MACI with scaffold A vs. MACI with scaffold B, OCA with cadaveric tissue vs synthetic tissue) with the exception of studies comparing first line procedure with second line procedure (e.g. first line OCA vs second line OCA after failed microfracture) • Waitlist control • No comparator

Outcomes	EQ:
	• Activity levels:
	  ○ Time to return to work or sport
	  ○ Rehabilitation time
	  ○ Activities of daily living
	• Patient-reported outcomes
	• Rates of retreatment
	• Avoidance of osteoarthritis and knee replacement
	
	SQ:
	• Serious adverse events (e.g., death, disability, cartilage or meniscal injury)
	• Adverse events (e.g., infection, bleeding, nerve damage, tendonitis, joint swelling or effusion)
	
	CQ: (U.S.-based cost inputs only)
	• Cost-effectiveness
	• Cost-utility
		• Intermediate outcomes, (e.g., imaging outcomes, pathology findings)
		• Non-validated measurement tool
		• Non-U.S. cost inputs

Timing & Language	• No timing restrictions • English-language articles	• No timing exclusions • Non–English language articles
Study Design	• EQ: RCTs, NRSI[a] • SQ: RCTs, NRSI • CQ: CEA, CUA, or CBA performed from the societal or payor perspective	• Editorials, commentaries, narrative reviews, or letters; conference abstracts; case reports or case series;; case-control studies; other observational study designs without a comparator group not already specified

PICOTS	Include	Exclude
		• Relevant systematic reviews will be excluded but will be hand searched to identify potentially eligible primary studies
Setting	• Countries categorized as "very high human development" on the United Nations Development Programme's 2018 Human Development Index Report[b]	• Countries not categorized as "very high human development" according to the United Nations Development Programme's 2018 Human Development Index Report[b]

Notes: [a]If insufficient RCT evidence is identified for the EQ, NRSIs will be included.
[b] Andorra, Argentina, Australia, Austria, Bahamas, Bahrain, Barbados, Belarus, Belgium, Brunei Darussalam, Bulgaria, Canada, Chile, Costa Rica, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hong Kong China (SAR), Hungary, Iceland, Ireland, Israel, Italy, Japan, Kazakhstan, Korea (Republic of), Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Montenegro, Netherlands, New Zealand, Norway, Oman, Palau, Panama, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Arab Emirates, United Kingdom, United States, and Uruguay.
Abbreviations: CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; CQ = cost question; CUA = cost-utility analysis; EQ = efficacy question; FDA= Food and Drug Administration; NRSI = nonrandomized study of intervention (e.g., prospective or retrospectively conducted comparative cohort study); RCT = randomized controlled trial; SQ = safety question

What is Excluded from this HTA

First and second generation ACI will not be an eligible procedure for this HTA as its use of a periosteal patch has evolved into MACI, which uses a porcine or synthetic matrix, reducing complications from ACI.[4,5] Exclusion of ACI limits the review to procedures typically performed in contemporary clinical practice. Studies that evaluate focal chondral defect procedures to restore the type of cartilage damage present in degenerative osteoarthritis will not be included. Case-control studies, case series, and case reports will not be included to ensure adequate comparative evidence is used in the evidence synthesis. While we will include comparative cohorts for the safety question, we will assess the body of trial evidence before considering the inclusion of comparative cohorts for efficacy.

Public Comments

The State of Washington's Health Technology Assessment Program posted for public comment the draft key questions and proposed scope for a health technology assessment (HTA) on the topic of "Treatment for Patients with Chondral Defects of the Knee" between December 22, 2023 and January 5, 2024. No public comments were received.

Washington State Health Care Authority

References

1. Heir S, Nerhus TK, Røtterud JH, et al. Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery. *Am J Sports Med.* 2010;38(2):231-237. PMID: https://www.ncbi.nlm.nih.gov/pubmed/20042546. doi: 10.1177/0363546509352157

2. Merkely G, Ackermann J, Lattermann C. Articular cartilage defects: incidence, diagnosis, and natural history. *Oper Tech Sports Med.* 2018;26(3):156-161. doi: 10.1053/j.otsm.2018.06.008

3. Oldershaw RA. Cell sources for the regeneration of articular cartilage: the past, the horizon and the future. *Int J Exp Pathol.* 2012;93(6):389-400. PMID: https://www.ncbi.nlm.nih.gov/pubmed/23075006. doi: 10.1111/j.1365-2613.2012.00837.x

4. Kon E, Filardo G, Di Matteo B, Perdisa F, Marcacci M. Matrix assisted autologous chondrocyte transplantation for cartilage treatment: a systematic review. *Bone Joint Res.* 2013;2(2):18-25. PMID: https://www.ncbi.nlm.nih.gov/pubmed/23610698. doi: 10.1302/2046-3758.22.2000092

5. Kon E, Filardo G, Di Martino A, Marcacci M. ACI and MACI. *J Knee Surg.* 2012;25(1):17-22. PMID: https://www.ncbi.nlm.nih.gov/pubmed/22624243. doi: 10.1055/s-0031-1299651