TREATMENT OF CARTILAGE LESIONS OF THE KNEE

Detroit, MI
July 18, 2018

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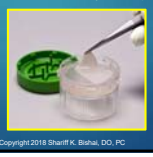
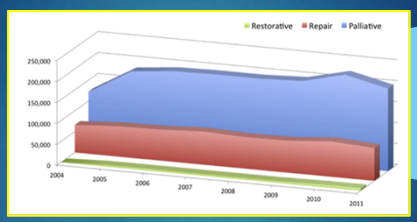
Past-President, Detroit Academy of Orthopaedic Surgery


Disclosures

- Paid Consultant
  - DePuy Synthes
  - Zimmer Biomet
  - Arthrex
  - Smith & Nephew
  - Ceterix
  - Trice Medical
  - Arthrosurface
  - Bard Davol
- Surgeon Advisory Boards
  - Mitek Sports Medicine

Trends of Cartilage Treatment



Restorative: Cartilage Reconstruction
Repair: Drilling and Microfracture
Palliation: Chondroplasty and Debridement

McCormick F, Harris JD, Abrams GD, Frank R, Gupta A, Hussey K, Wilson H, Bach B, Cole B. Trends in Surgical Treatment of Articular Cartilage Lesions in the United States: An Analysis of a Large Private-Payer Database Over a Period of 8 Years. Arthroscopy. 30: 2, 222-226.

Osteochondral Allografts History

- Use of Osteochondral Allografts was first described by Erich Lexer in 1908
- Present Indications:
  - Osteonecrosis
  - Post-traumatic reconstruction
  - Osteochondritis dissecans Type III or IV
  - Chondral or osteochondroal lesions greater than 2 cm
  - Revision or salvage of other cartilage surgery

Photo courtesy of Erich Lexer Klinik

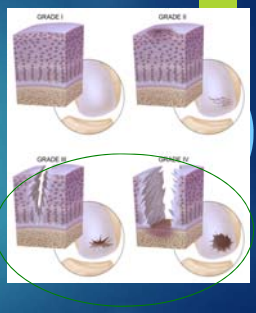
Patient Workup

- Radiographs
  - Weight Bearing Films
    - Show Loss of Cartilage Space
  - Full-Length Mechanical Axis Films
    - Show Alignment
- MRI
  - Provides Information About:
    - Articular Cartilage
    - Ligaments
    - Meniscus
- CT
  - Patellofemoral Tracking
- Dynamic CT/MRI
- dGEMRIC

Osteochondral Allografts

Osteochondral Allografts Indications

- Indications for Osteochondral Allografts
  - Repair of Chondral Defects with Bony Involvement, Osteochondral Defects or Lesions
  - Revision of Failed Prior Cartilage Procedures
    - Especially in the Setting of Altered Subchondral Bone
  - Can Be Used in Any Diarthrodial Joint
  - Multiple Allografts May Be Implanted to Fill Irregularly-Shaped or Lesions > 2cm²



Condyle-Specific Matching Does Not Improve Midterm Clinical Outcomes of Osteochondral Allograft Transplantation in the Knee

Wang, Dean MD[1,4]; Jones, Kristofer J. MD[2]; Eliasberg, Claire D. MD[1]; Pais, Mollyann D. BS[1]; Rodeo, Scott A. MD[1]; Williams, Riley J. III MD[3]

JBJS: October 4, 2017 - Volume 99 - Issue 19 - p 1614–1620
doi: 10.2106/JBJS.16.01542

Background: Condyle-specific matching for osteochondral allograft transplantation (OCA) pairs donor and recipient condyles in an attempt to minimize articular incongruity. While the majority of cartilage defects are located on the medial femoral condyle, lateral femoral condyles are more commonly available as a graft source. The purpose of this study was to compare the clinical outcomes of patients treated with non-orthotopic (lateral-to-medial condyle or medial-to-lateral condyle) OCA with those treated with traditional orthotopic (medial-to-medial condyle or lateral-to-lateral condyle) OCA. We hypothesized that clinical outcomes would be similar between groups at midterm follow-up.

Size matching with condyle specific matching is unnecessary and therefore off the shelf allografts are a good option for cartilage reconstruction

demonstrated significant increases in the Short Form-36 (SF-36) physical functioning and pain, International Knee Documentation Committee (IKDC), and Knee Outcome Survey-Activities of Daily Living (KOS-ADL) scores compared with baseline ($p < 0.004$). Outcome scores (baseline and postoperative) and change scores did not differ significantly between groups.

Conclusions: Clinical outcomes do not differ between patients treated with orthotopic OCA and those treated with non-orthotopic OCA, suggesting that condyle-specific matching may not be necessary.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Osteochondral Allografts Chondrofix

Chondrofix® Osteochondral Allograft

Biologic Treatment for Early Intervention and Cartilage Repair

Osteochondral Solutions
Off the Shelf Allografts

- Chondrofix® is a sterile, decellularized osteochondral allograft (OCA) often in a pre-shaped cylindrical form
- Composed of decellularized hyaline cartilage and cancellous bone
- Osseus portion serves as an osteoinductive scaffold

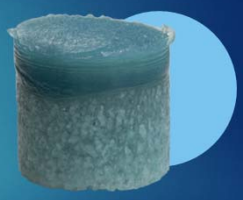
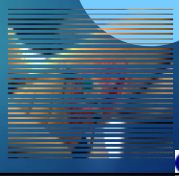


Image Courtesy of Zimmer Biomet

Osteochondral Allografts
Off the Shelf Allografts

- Chondrofix
  - Biologic Implant
    - Osteochondral Allograft
    - Composed of Decellularized Hyaline Cartilage and Cancellous Bone
    - 7mm, 9mm, 11mm and 15mm Diameters
      - Pre-cut in 10mm Lengths
    - Pre-Packaged, Off-the–Shelf Product
    - Sterile, Viral Inactivated
    - Long Shelf Life, 18-24 months
    - Similar Mechanical Properties as Fresh Osteochondral Tissue



Osteochondral Allografts
Chondrofix

Recovery

- Human tissue is recovered by an accredited tissue bank.
- Strict requirements have been specified to ensure highest quality donor tissue

Processing

- Tissue undergoes processing protocol that maintains biomechanical stability of tissue .
- Grafts are viral inactivated to remove viruses to non-traceable levels.
- Delipidization process.

Chondrofix®

- Grafts are packaged and terminally sterilized to provide off-the-shelf convenience.
- Grafts can be stored at room temperature for up to 18-24 months.

Orthop J Sports Med. 2015 Jul; 3(7 suppl2): 2325967115S00068. PMCID: PMC4901625
Published online 2015 Jul 17. doi: 10.1177/2325967115S00068

Decellularized Osteochondral Allograft for the Treatment of Cartilage Lesions in the Knee

Jack Farr, MD,[1] Guilherme Gracitelli, MD,[2] and Andreas H. Gomoll, MD[3]

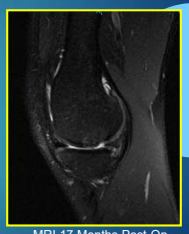
- Prospective Case Series of 32 patients treated with a Chondrofix ® implant for OCD lesions of the knee
  - 24 (75%) of the knees had previous surgery
  - Mean defect area was 2.9cm +/- 2.0 cm
  - Mean allograft size was 13.18 +/- 2.3mm
- Failure defined as graft structural damage on arthroscopy or repeat MRI leading to removal of the OCA

Results
- 23 of 32 knees (72%) failed and 14 of 32 knees (43%) required further surgery
- Implant survivorship was 19.6% at 2 years

15 yo, ACL Revision Reconstruction, MFC OCD, Meniscal Tear


15 yo, ACL Revision Reconstruction, MFC OCD, Meniscal Tear


MRI 5 Months Post-Op

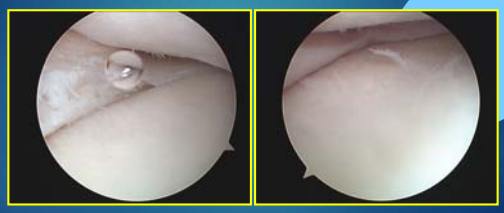

MRI 17 Months Post-Op

15 yo, ACL Revision Reconstruction, MFC OCD, Meniscal Transplant

5 Months Post-Op

17 Months Post-Op

17 yo, ACL Tunnel Grafting, MFC OCD, Meniscal Allograft



17 yo, ACL Tunnel Grafting, Second/Third Looks

Second Look 15-mm Chondrofix at 18 Months

Third Look 15-mm Chondrofix at 25 Months

Arthrex / JRF Pre-Cut Osteochondral Allografts

Fresh Frozen Precut Allograft Plugs

- Size
  - 10mm x 12mm
  - 15mm x 12mm
- Viable Hyaline Cartilage
  - 80% Viable Chondrocytes
- Basic Technique and Instrumentation
  - Single stage no patient matching required
  - Arthrex OATS 10mm instrumentation or Large OATS Instrumentation
- 28 day Shelf-life

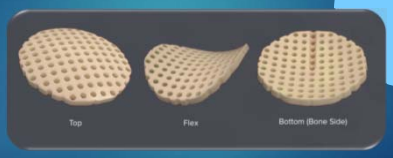
Cartiform®

Viable Osteochondral Allograft

- What is Cartiform?
  - Cryopreserved Osteochondral Allograft
  - Retains endogenous chondrocytes, ECM, growth factors
- How is Cartiform recovered?
  - Osteochondral allograft is recovered from condyle
  - Bony layer reduced to minimal
  - Graft is porated then cryopreserved
- Why is the graft porrous?
  - Increase flexibility
  - Enhance cryopreservation of native chondrocytes
  - Facilitate mesenchymal stem cell migration into Cartiform following marrow stimulation procedure
- How is Cartiform intended to be used?
  - Restore articular surface in osteochondral lesions with minimal bony involvement.

Cartiform®
Viable Osteochondral Allograft

- ✓ Flexible to match anatomical contours
- ✓ Trimmable to fit any articular lesion size



Cartiform®
Viable Osteochondral Allograft

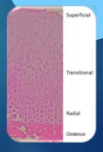
- ✓ Flexible to match anatomical contours
- ✓ Trimmable to fit any articular lesion size
- ✓ Versatile fixation techniques: Anchors or Suture
- ✓ "Off-the-Shelf" option

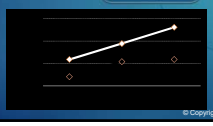
Cartiform®
Viable Osteochondral Allograft

Cell

Signal

Scaffold





Fresh Precut + BioCartilage

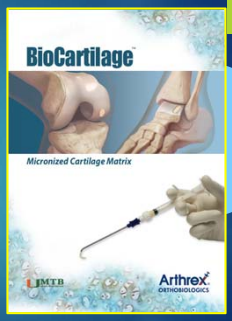
Courtesy Jason Scopp, MD

Articular lesion in MFC. Planned Fresh Precut, lesion was larger than anticipated.

Augmented with BioCartilage.

Arthrex® BioCartilage™

- Allograft Cartilage from Adult Donors
  - Dehydrated
  - Micronized
- Principle is to Serve as a Scaffold over a Microfractured defect
  - Provides Tissue Network that can Potentially Signal Autologous Cellular Interactions
  - Improve the Degree and Quality of Tissue Healing within a Properly Prepared Articular Cartilage Defect



Arthrex Collateral Information. www.arthrex.com

Osteochondral Allograft Data

MOST, IF NOT ALL DATA, IS BASED ON FRESH, FROZEN ALLOGRAFTS

Osteochondral Allograft Transplantation of the Knee

Analysis of Failures at 5 Years

Rachel M. Frank,* MD, Simon Lee,* MD, MPH, David Levy,* MD, Sarah Poland,* BA, Maggie Smith,* BS, Nina Scalise,* BS, Gregory L. Cvetanovich,* MD, and Brian J. Cole,*† MD, MBA
Investigation performed at Rush University Medical Center, Chicago, Illinois, USA

- Level IV case series
- Prospective review of 180 patients receiving OCA procedure
  - One institution by a single surgeon meeting inclusion criteria
  - 24 patients (13%) considered failures at a mean of 3.7 +/- 2.6 years after index OAT procedure
- Failures led to revision OCA (N=7), conversion to TKA (N=12) or degraded graft during arthrsocopy (N=5).
- Statistically and clinically significant improvements in Lysholm score, KOOS score, and International Knee Documentation Committee score excluding failures (P<.001)

Systematic Review

Long-term Outcomes After Osteochondral Allograft: A Systematic Review at Long-term Follow-up of 12.3 Years

Andrew T. Assenmacher M.D. [a], Ayoosh Pareek B.S. [a], Patrick J. Reardon B.S. [a], Jeffrey A. Macalena M.D. [b], Michael J. Stuart M.D. [a], Aaron J. Krych M.D. [a]

- Systematic review of 5 studies totaling 291 patients
  - Average age of 34.8 years
- Mean failure rate of 25% at 12.3 years with a reoperation rate of 36%
- 72% of failures were converted to a TKA (68%) and UKA (4%)
- 28% of failures required graft removal, fixation, or revision
- Patellofemoral lesions led to a higher failure rate of 83% than lesion in the femoral condyles or tibial plateau (P=.01)

Is Return to Play Affected by Osteochondral Allografts?

Arthroscopy. 2017 Sep;33(9):1712-1717. doi: 10.1016/j.arthro.2017.03.020.

Can Competitive Athletes Return to High-Level Play After Osteochondral Allograft Transplantation of the Knee?

McCarthy MA[1], Meyer MA[1], Weber AE[1], Levy DM[1], Tilton AK[1], Yanke AB[1], Cole BJ[2].

- Retrospective review of competitive high school, collegiate, and professional athletes undergoing OCA transplantation of the knee and RTP
  - Patients undergoing isolated femoral condyle OCA from 2004-2013

Results

- 13 patients (4 intercollegiate, 9 high school) identified with mean follow-up of 5.9 +/-2.5 years
- 7 athletes (54%) returned to competitive sport at 7.9 +/- 3.5 months
  - 5 patients returned to pre-injury level on KOOS and WOMAC scores
- Adjusted RTP of 10 patients (77%) who competitively RTP or thought they could have if they had not graduated
- 3 reoperations at an average of 3.8 +/-3.3 years with no graft failures

- Can the addition of Bone Marrow Aspirate Concentrate help to integrate the graft into host tissue after implantation?

Osteochondral Allografts Incorporation

- Incorporation of Osteochondral Allografts Occurs in 3 Phases
  - Phase 1
    - Vascular Ingrowth
    - Infiltration of Mesenchymal Cells
  - Phase 2
    - Osteoblastic Appositional New Bone Formation Onto Bone Graft Trabeculae
  - Phase 3
    - Bone Remodeling to Produce Mature Trabecular Pattern
- Cancellous Allografts Incorporate 50% Slower than Autografts

Day M, Osthum RF, Chao EYS, Rubin CT, Aro HT, Einhorn TA. Bone injury, regeneration, and repair. In: Orthopaedic Basic Science. 2nd ed. Eds: Buchwalter JA, Einhorn TA, Simon SR. American Academy of Orthopaedic Surgeons, 2000.

Am J Sports Med. 2017 Jul 1:363546517715725. doi: 10.1177/0363546517715725. [Epub ahead of print]

Effects of Autogenous Bone Marrow Aspirate Concentrate on Radiographic Integration of Femoral Condylar Osteochondral Allografts.

Oladeji LO[1], Stannard JP[1,2], Cook CS[1,2], Kfuri M[1], Crist BD[1], Smith MJ[1], Cook JL[1,2].

- Level III Cohort study of patients requiring transplantation of large OCAs to one or both femoral condyles at one institution from 2013-2016
- Patients stratified to BMAC treatment vs no treatment
- Independent musculoskeletal radiologist blinded to treatment group and time point
- Degree of integration and amount of sclerosis measured

Am J Sports Med. 2017 Jul 1:363546517715725. doi: 10.1177/0363546517715725. [Epub ahead of print]

Effects of Autogenous Bone Marrow Aspirate Concentrate on Radiographic Integration of Femoral Condylar Osteochondral Allografts.

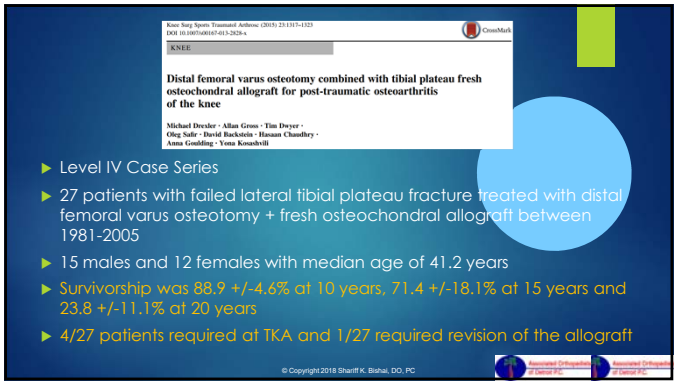
Oladeji LO[1], Stannard JP[1,2], Cook CS[1,2], Kfuri M[1], Crist BD[1], Smith MJ[1], Cook JL[1,2].

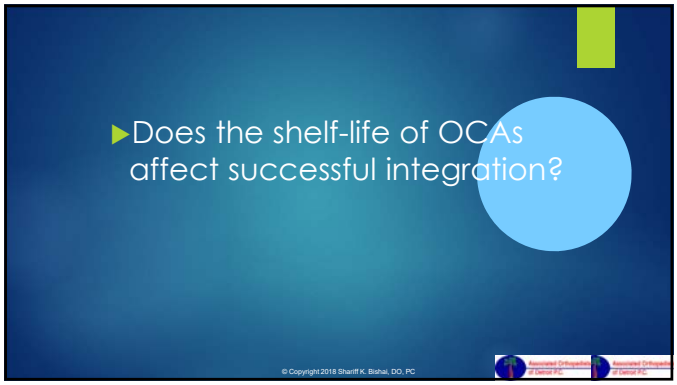
Results

- 17 condyles in 15 patients undergoing [illegible] BMC and 29 condyles in 22 patients [illegible]
- BMC group had a signif[illegible] graft integration at 6 weeks, 3 months [illegible] post-op (P = 0.33)
- Graft scle[illegible]y less pronounced in BMC group at the [illegible]ove (P=.017)

Conclusion: Large femoral condylar OCAs treated with autogenous BMC before implantation showed superior radiographic integration to bone and less sclerosis during the initial 6-month postoperative period. BMC treatment of OCAs may mitigate the failure of OCA bone healing.

- Do other combined procedures at time of index osteochondral allograft transplantation lead to more successful graft incorporation?


Knee Surg Sports Traumatol Arthrosc (2015) 23:1317–1323
DOI 10.1007/s00167-013-2828-x
KNEE
Distal femoral varus osteotomy combined with tibial plateau fresh osteochondral allograft for post-traumatic osteoarthritis of the knee
Michael Drexler · Allan Gross · Tim Dwyer · Oleg Safir · David Backstein · Hasaan Chaudhry · Anna Goulding · Yona Kosashvili
Level IV Case Series
27 patients with failed lateral tibial plateau fracture treated with distal femoral varus osteotomy + fresh osteochondral allograft between 1981-2005
15 males and 12 females with median age of 41.2 years
Survivorship was 88.9 +/-4.6% at 10 years, 71.4 +/-18.1% at 15 years and 23.8 +/-11.1% at 20 years
4/27 patients required at TKA and 1/27 required revision of the allograft
© Copyright 2018 Shariff K. Bishai, DO, PC


Does the shelf-life of OCAs affect successful integration?
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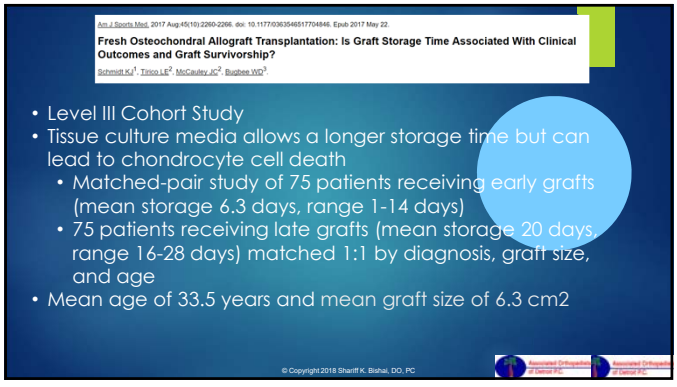

Am J Sports Med. 2017 Aug;45(10):2260-2266. doi: 10.1177/0363546517704846. Epub 2017 May 22.
Fresh Osteochondral Allograft Transplantation: Is Graft Storage Time Associated With Clinical Outcomes and Graft Survivorship?
Schmidt KJ[1], Tirico LE[2], McCauley JC[2], Bugbee WD[3]
Level III Cohort Study
Tissue culture media allows a longer storage time but can lead to chondrocyte cell death
Matched-pair study of 75 patients receiving early grafts (mean storage 6.3 days, range 1-14 days)
75 patients receiving late grafts (mean storage 20 days, range 16-28 days) matched 1:1 by diagnosis, graft size, and age
Mean age of 33.5 years and mean graft size of 6.3 cm2
© Copyright 2018 Shariff K. Bishai, DO, PC

Am J Sports Med. 2017 Aug;45(10):2260-2266. doi: 10.1177/0363546517704846. Epub 2017 May 22.

Fresh Osteochondral Allograft Transplantation: Is Graft Storage Time Associated With Clinical Outcomes and Graft Survivorship?

Schmidt KJ[1], Tirico LE[2], McCauley JC[2], Bugbee WD[3]

- All patients had minimum 2 year follow-up
- OCA failure found in 25.3% (19/75) of patients in the early release group and 12% (9/75) in the late release group (P=.036)
- 5 years survivorship was 85% for the early release group and 90% for the late release group (P=.321)
- No difference in pain and function was found between the two groups

Osteochondral Allografts - Summary

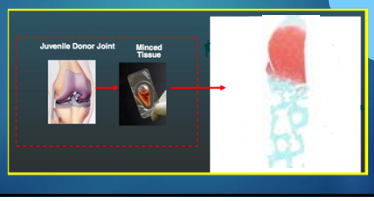
- Success rate high at both 5 years (87%) and 12 years (75%) in the studies described above
- A large number of competitive athletes return to play after osteochondral allograft (between 54-77%)
- Bone Marrow Aspirate Concentrate seems to help incorporation of the graft
- Newer tissue culture media and preservation methods show that prolonged storage leads to similar outcomes as fresh and early grafts
- Fix the environment --- Alignment
- More higher level studies needed

Cell-based Cartilage Reconstruction

DeNovo® NT Natural Tissue Graft

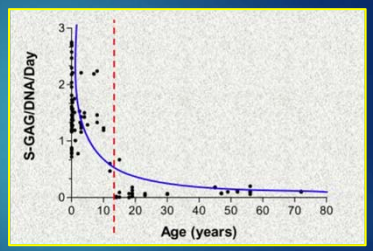
DeNovo NT Graft

- Cartilage Tissue Allograft Composed of Juvenile Donor Hyaline Cartilage Pieces
  - Mechanically Minced
  - Inclusive of Viable Cells
- Secured Into Cartilage Defects with Fibrin Adhesive



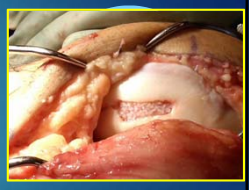
DeNovo NT Graft

- Juvenile Allograft Cartilage
  - From Donors <13 Years Old
    - Viable Chondrocytes
- Single Stage Procedure
- No Donor Site Issues
- Repair Tissue Shows Growth and Autocontouring



DeNovo® NT Natural Tissue Graft

- Allograft Tissue Derived from Juvenile Articular Cartilage
  - Processed by AlloSource, Denver , CO
  - Aseptically Processed and Packaged
- Primary use in:
  - Distal Femur (Especially MFC)
  - Patella
  - Talus
- Each Unit Sufficient For 2.5cm^2 Lesion



DeNovo® NT Natural Tissue Graft

- First implanted in May 2007 by Dr Kevin Bonner, Virginia Beach, VA
- DeNovo NT is Regulated as a Tissue
- Extensive and Continuing Clinical Studies
  - Prospective 25 Patient Cohort in Knee Lesions (complete)
  - Longitudinal Study in Knee (98 lesions), Ongoing and Data Available
  - Longitudinal Study in Ankle (157 lesions), Ongoing and Data Available

DeNovo® NT Natural Tissue, Rationale for Use

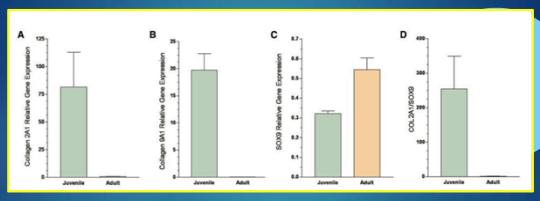
- Juvenile Chondrocytes Express Significantly More GAGs than Adult
  - Other Work on Bovine Cartilage Tissue Presented Separately
- The Tissue is Immune Privileged and No Reactions or Rejections Have Been Noted
- No Harvesting of Periosteum Required
- Fixed with Fibrin Adhesive
- Single Stage Surgery

DeNovo NT Graft

- Juvenile Cartilage Cell Density is 10 Times Greater Than Adult Cartilage Cell Density

DeNovo NT Graft

Gene Expression: Juvenile vs. Adult

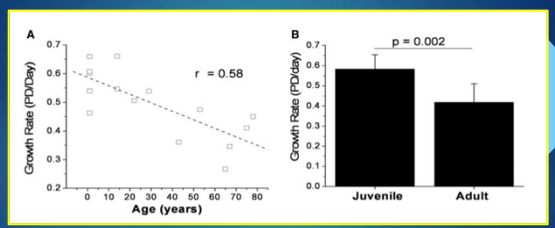


100-700-fold Greater Amounts of mRNA for Type II (A) and Type IX (B) Collagen from Juvenile vs. Adult Human Articular Cartilage

Adkisson HD, Martin JA, Amendola RL et al. The Potential of Human Allogenic Juvenile Chondrocytes for Restoration of Articular Cartilage. Am J Sports Med 2010; 38 (7): 1324-1333.

DeNovo NT Graft

Chondrocyte Growth Rate: Juvenile vs. Adult



Mean Growth Rate for Juvenile Cells was Significantly Greater than for Adults (P=0.002)

Adkisson HD, Martin JA, Amendola RL et al. The Potential of Human Allogenic Juvenile Chondrocytes for Restoration of Articular Cartilage. Am J Sports Med 2010; 38 (7): 1324-1333.

DeNovo NT

sGAG Content: Bovine Model - Juvenile vs. Adult

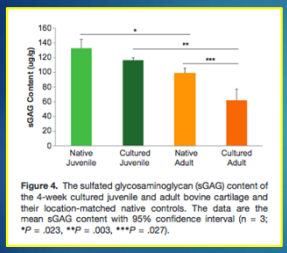


Figure 4. The sulfated glycosaminoglycan (sGAG) content of the 4-week cultured juvenile and adult bovine cartilage and their location-matched native controls. The data are the mean sGAG content with 95% confidence interval (n = 3; *P = .023, **P = .003, ***P = .027).

- Compared with Adult Cartilage
  - Significantly Greater Cell Density
  - Higher Cell Proliferation Rate
  - Increased Cell Growth
  - Elevated GAG content
  - Enhanced Matrix Metallopeptidase 2 Activity

Liu H, Zhao J, Clarke RB, Goo J, Garrett IR, Margerrison EE. Enhanced Tissue Regeneration Potential of Juvenile Articular Cartilage. Am J Sports Med 2013; 41 (11): 2658-2667.

DeNovo NT

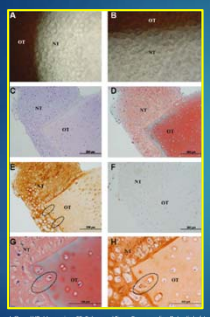
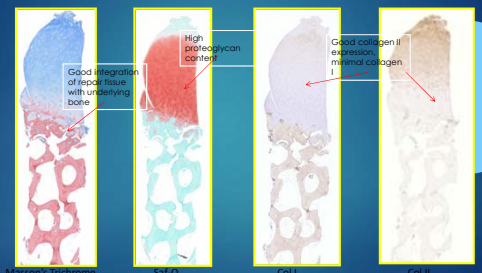


Figure 3. Formation of new tissue structure from juvenile cartilage discs. The new tissue generated around the inner margin (A, 20×) and the outer margin (B, 20×) demonstrated similar patterns as the original cartilage on H&E (C), safranin O (D), type II collagen (E), and type I collagen (F) staining. Both safranin O (G) and type II collagen (H) staining demonstrated local ECM disruptions at the chondrocyte migration front and the formation of migrating channels (indicated by circles). NT, new tissue; OT, original tissue.

Liu H, Zhao J, Clarke RB, Goo J, Garrett IR, Margerrison EE. Enhanced Tissue Regeneration Potential of Juvenile Articular Cartilage. Am J Sports Med 2013; 41 (11): 2658-2667.

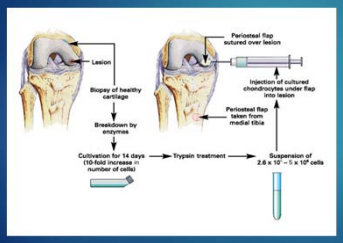
Histology of *DeNovo* NT Graft at 2 yrs Post Op

37 yo Male, 3.4 cm² MFC lesion, Prior MFX



History of ACI

First-Generation: Periosteal Membrane



Challenges

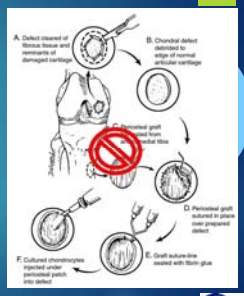
- Time consuming and technically demanding to harvest/suture periosteum
- Periosteal tissue consistency/predictability
- Periosteal donor site morbidity
- Distribution of implanted chondrocytes
- Larger incisions
- Periosteal hypertrophy

History of ACI

Second-Generation: Collagen Membrane

Challenges

- Time consuming and technically demanding to suture collagen membrane
- Distribution of implanted chondrocytes



Third Generation: MACI

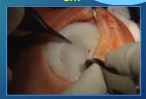
MACI® (autologous cultured chondrocytes on porcine collagen membrane):

- First FDA-approved cellularized scaffold using tissue engineering principles (BLA December 13, 2016)

Less Invasive

Sutures Not Required

Chondrocytes uniformly seeded at a density of 500,000 to 1,000,000 cells per cm²



[1] Study ID: MACI 02206: A Prospective Randomized Open-label Parallel-group Multi-center Study to Demonstrate the Superiority of Matrix-induced Autologous Chondrocyte Implantation (MACI®) Versus Arthroscopic Microfracture for the Treatment of Symptomatic Articular Cartilage Defects of the Femoral Condyle Including the Trochlea.

[2] MACI implants for SUMMIT manufactured in Cambridge, MA, USA

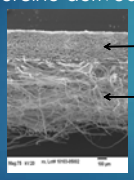
MACI Description

Implant measures
5cm wide x 3cm long

Orientation notch:
- Measures 0.5cm x 1.0cm
- Removed from lower left indicating cell side up

MACI Description

Cultured Chondrocytes placed on a Resorbable porcine derived Type I/III collagen membrane

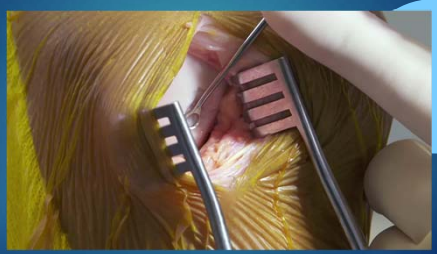


Dense collagen fibers form smooth, lower friction surface which faces joint.

Less dense / porous surface provides opportunity for chondrocyte adherence

Chondrocyte attached to collagen fiber

Debridement



Sizing and Shaping

Implantation

Why not try Microfracture First?

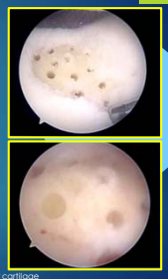
Microfracture is Not a Benign Procedure

- Mithoefer et al, 2005
  - 30-50% of Patients With Previous Failed Marrow Stimulation Procedures Had Altered Subchondral Bone
    - Microfracture
    - Drilling
    - Abrasion Arthroplasty

Mithoefer K, Williams RJ 3rd, Warren RF, Potter HG, Spock CR, Jones EC, Wickiewicz TL, Marx RG (2005) The microfracture technique for the treatment of articular cartilage lesions in the knee. A prospective cohort study. J Bone Joint Surg Am 87:1911–1920

Microfracture is Not a Benign Procedure

- Mithofer et al, 2009
  - Factors for better outcomes[1,2]
    - Age < 40 years
    - Preoperative symptoms < 12 months
    - Lesion size
      - Nonathletes: ≤ 4cm²
      - Athletes: < 2cm²
      - BMI < 30 kg/m²



1. Mithoefer K, McAdams T, Williams RJ, et al. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. *Am J Sports Med*. 2009;37:2053–2063.
2. Goyal D, Keyhani S, Lee EH, et al. Evidence-based status of microfracture technique: a systematic review of level I and II studies. *Arthroscopy*. 2013;29:1579–1588

Microfracture is Not a Benign Procedure

- Microfracture is not a benign procedure
  - Goyal et al. *Arthroscopy* 2013
    - At one year, subchondral cysts were noted in 33% of patient's treated with microfracture
    - 33% of patients were found to have early arthritis after microfracture for lesions > 4cm² 5 years after the procedure

Goyal D, Keyhani S, Lee EH L, Hui JH o. P. Evidence-based status of microfracture technique: a systematic review of level I and II studies. *Arthroscopy*. 2013;29(9):1579-1588.

- So microfracture failed, does it lead to issues with subsequent procedures?

ACI after Failed Marrow Stimulation

Minas et al. *Am J Sports Med.* 2009

- Prospective cohort study – Level 2
- 321 patients (325 knees) treated with ACI
- Grouped by history of prior MST/no prior MST

Increased Failure Rate of Autologous Chondrocyte Implantation After Previous Treatment With Marrow Stimulation Techniques

Tom Minas,* MD, MS, Andreas H. Gomoll, MD, Ralf Rosenberger, MD, Ronald O. Royce, DO, and Tim Bryant, RN
From the Cartilage Repair Center, Department of Orthopaedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

MST = Marrow Stimulation (microfracture, abrasion arthroplasty, drilling)

Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. *Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. Am J Sport Med.* 2009;37(5):902-908.

ACI after Failed Marrow Stimulation

Minas et al. *Am J Sports Med.* 2009

	No MST	Prior MST	P
Knees (patients), n	214 (211)	111 (110)	--
Ave. Age, y (SD, range)	35.0 (9.2, 13-60)	35.4 (10.1, 14-55)	.7
Gender, men/women, n	124/87	61/49	.6
Ave. F/U time, mo, (SD, range)	54 (27, 24-132)	56 (30, 24-144)	.4
Ave. No. defects/knee (SD, range)	1.7 (0.9, 1-5)	1.7 (0.8, 1-4)	.9
Ave. Defect Size, cm^2 (SD, range)	4.6 (2.7, 0.5-21)	5.2 (3.1, 0.7-16.8)	.2
Ave. Tx area/knee, cm^2 (SD, range)	7.9 (5.0, 1.0-28.3)	8.6 (5.9, 1.5-30.5)	.3
Workers' Comp. patients, n (%)	28 (13)	24 (22)	.1

Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. *Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. Am J Sport Med.* 2009;37(5):902-908.

ACI after Failed Marrow Stimulation

Minas et al. *Am J Sports Med.* 2009

	No Prior MST No. Failures (%)	Prior MST No. Failures (%)
Overall	17/214 (8)	29/111 (26)
Simple Defects	2/18 (11)	1/9 (11)
Complex Defects	9/97 (9)	17/56 (30)
Salvage Defects	6/99 (6)	11/46 (24)

MST = Marrow Stimulation (microfracture, abrasion arthroplasty, drilling)

Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. *Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. Am J Sport Med.* 2009;37(5):902-908.

ACI After Failed Marrow Stimulation

Zaslav et al. *Am J Sports Med* 2008

- Prospective Cohort – Level 2
- 126 patients with failed treatment for articular cartilage defects of the knee were treated with ACI
  - Microfracture 42 (27%)
  - Subchondral Drilling 16 (10%)
  - Abrasion Arthroscopy 9 (6%)
  - MST unspecified 1 (0.6%)

MST: marrow stimulation technique

Zaslav K, Cole B, Brewster R, et al. A prospective study of autologous chondrocyte implantation in patients with failed prior treatment for articular cartilage defect of the knee: results of the Study of the Treatment of Articular Repair (STAR) clinical trial. *Am J Sports Med.* 2009;37(1):42-55.

ACI After Failed Marrow Stimulation

	MST (n=69) Baseline	MST (n=69) Month 48	Debridement (n=74) Baseline	Debridement (n=74) Month 48
Modified Cincinnati Mean (SD)	3.2 (1.1)	6.4 (2.3)[a]	3.4 (1.0)	6.2 (2.3)[a]
KOOS				
Pain Mean (SD)	49.9 (14.5)	74.6 (20.0)[b]	48.0 (17.5)	70.8 (20.0)[b]
Symptoms Mean (SD)	53.0 (17.3)	72.7 (17.5)[b]	51.9 (19.8)	70.1 (19.6)[b]
Sports/Rec Mean (SD)	30.2 (27.2)	57.7 (31.0)[b]	22.3 (19.5)	56.3 (27.9)[b]
ADL Mean (SD)	59.4 (18.1)	82.1 (19.0)[b]	58.5 (21.0)	80.7 (18.2)[b]
QoL Mean (SD)	20.7 (15.6)	53.2 (26.2)[b]	21.5 (14.8)	51.1 (24.0)[b]

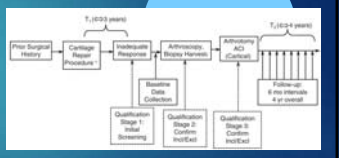
[a]Indicates ≥2 point improvement in Modified Cincinnati score.
[b]Indicates ≥10 point change in KOOS score

Zaslav K, Cole B, Brewster R, et al. A prospective study of autologous chondrocyte implantation in patients with failed prior treatment for articular cartilage defect of the knee: results of the Study of the Treatment of Articular Repair (STAR) clinical trial. *Am J Sports Med.* 2009;37(1):42-55.

ACI After Failed Marrow Stimulation

Zaslav et al. *Am J Sports Med* 2008

- Both groups had similar improvement in the overall Cincinnati score from baseline to 48 months
- Both groups had similar improvement in al 5 categories of the KOOS scale
- Similar proportion of patient's met the a priori definition of treatment failure post-ACI
  - 25% (17/69) in the MST cohort
  - 26% (19/74) in the debridement cohort
- No statistically significant difference in the durability of ACI after MST (>34.0 months) vs. that of ACI after debridement (>36.4 months)



Zaslav K, Cole B, Brewster R, et al. A prospective study of autologous chondrocyte implantation in patients with failed prior treatment for articular cartilage defect of the knee: results of the Study of the Treatment of Articular Repair (STAR) clinical trial. *Am J Sports Med*. 2009;37(1):42-55.

ACI after Failed Microfracture

Pestka et al. *Am J Sports Med* 2012

- Matched-pair cohort study – Level 3
- 56 patients total (28 per group)
  - Group A: history of failed microfracture
    - Mean Follow-up 48.0 months
  - Group B: ACI used as a first-line treatment
    - Mean follow-up 41.4 months

Pestka JM, Bode G, Salzmann G, Südkamp NP, Niemeyer P. Clinical Outcome of Autologous Chondrocyte Implantation for Failed Microfracture Treatment of Full-Thickness Cartilage Defects of the Knee Joint. *Am J Sports Med*. 2012;40(2):325-331.

ACI after Failed Microfracture

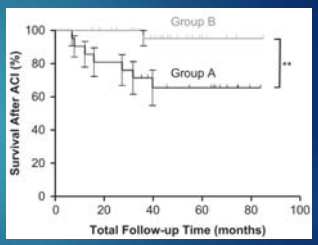
	Group A	Group B	*P* Value
No. of patients	27	28	
IKDC score, mean ± SD	58.4 ± 22.4	69.0 ± 19.1	.058
KOOS score, mean ± SD			
Symptoms	72.7 ± 22.3	80.0 ± 16.7	.088
Pain	69.2 ± 25.6	80.1 ± 16.4	.034[a]
Sports/Recreation	43.7 ± 31.3	56.4 ± 28.4	.061
ADL	78.5 ± 19.3	86.3 ± 14.3	.024[a]
QOL	41.5 ± 24.5	48.9 ± 23.7	.133
VAS pain before ACI, mean ± SD	3.4 ± 1.9	4.4. ± 2.5	.014[a]
VAS function after ACI, mean ± SD	6.2 ± 2.3	6.9 ± 2.2	.032[a]

IKDC: International Knee Documentation Committee, KOOS: Knee Injury and Osteoarthritis Score, ADL: Activities of Daily Living, QOL: Quality of Life, VAS: Visual Analog Scale

Pestka JM, Bode G, Salzmann G, Südkamp NP, Niemeyer P. Clinical Outcome of Autologous Chondrocyte Implantation for Failed Microfracture Treatment of Full-Thickness Cartilage Defects of the Knee Joint. *Am J Sports Med*. 2012;40(2):325-331.

ACI after Failed Microfracture

- Once a microfracture procedure has failed, treatment options are limited
- "…ACI even in this setting is able to provide satisfactory clinical results, as measured by the IKDC and KOOS."
- Changes is sporting activity "were equally pronounced in both groups despite the significantly higher failure rate found in group A."

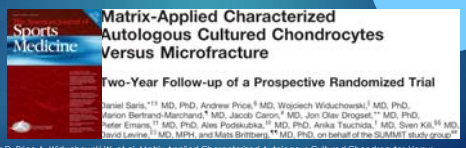


Peskta JM, Bode G, Salzmann G, Südkamp NP, Niemeyer P. Clinical Outcome of Autologous Chondrocyte Implantation for Failed Microfracture Treatment of Full-Thickness Cartilage Defects of the Knee Joint. *Am J Sports Med*. 2012;40(2):332-331.

MACI After Prior Cartilage Surgery

Saris et al. *Am J Sports Med* 2014

- Randomized control trial – Level 1
- 137 patients treated with MACI or microfracture completed 2-year follow-up



Saris D, Price A, Widuchowski W, et al. Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Two-Year Follow-up of a Prospective Randomized Trial. *Am J Sports Med*. 2014;42(6):1384-1394.

MACI After Prior Cartilage Surgery

Saris et al. *Am J Sports Med* 2014

- Marrow stimulation accounted for 21/65 (32%) of patients with prior cartilage surgery

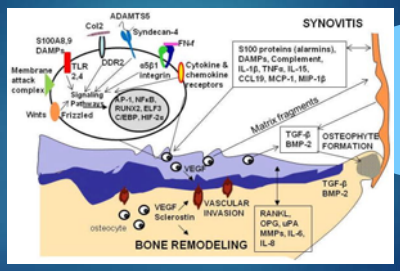
		Response Rates*, % patients (n/N)	
		MACI	Microfracture
Overall		87.5 (63/72)	68.1 (49/72)
Prior Cartilage Surgeries	No	90.0 (27/30)	74.2 (23/31)
	1	87.0 (20/23)	67.9 (19/28)
	>1	84.2 (16/19)	53.9 (7/13)

*Patients were considered responders if they had ≥10-point improvement over baseline in KOOS pain and function scores

Saris D, Price A, Widuchowski W, et al. Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Two-Year Follow-up of a Prospective Randomized Trial. *Am J Sports Med*. 2014;42(6):1384-1394.

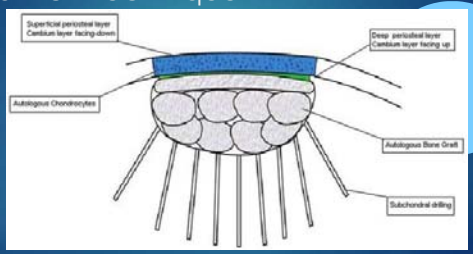
- What if there is bony involvement with the cartilage injury?

Knee as an Organ



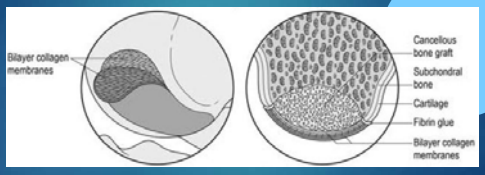
Widmaier EP; Raff H; Strang KT (2014). *Vander's Human Physiology* (12th ed.)

First Generation ACI Sandwich Technique



Peterson L, Jones DG. Autologous Chondrocyte Implantation (ACI): Jahrbuch. 2006;88-A:2502-2520.

MACI Sandwich Technique



Vijayan S, Bartlett W, Bentley G, et al. Autologous chondrocyte implantation for osteochondral lesions in the knee using a bilayer collagen membrane and bone graft: a two- to eight-year follow-up study. *J Bone Joint Surg Br.* 2012;94(4):488-492.

First Generation ACI Sandwich Technique

Peterson L, Minas T, Brittberg M et al. *J Bone Joint Surg Am.* 2003

- 58 patients with radiographic documentation of OCD treated with ACI
- Subset of patients with lesions >10mm treated with sandwich technique
- Mean lesion size: 5.7cm^2
- Mean follow up: 5.6 years

Peterson L, Minas T, Brittberg M, et al. Treatment of osteochondritis dissecans of the knee with autologous chondrocyte transplantation: results at two to ten years. *J Bone Joint Surg Am.* 2003; 85-A (suppl 2):17-24.

First Generation ACI Sandwich Technique

Peterson L, Minas T, Brittberg M et al. *J Bone Joint Surg Am.* 2003

- Results
  - 91% of patients had good to excellent rating on clinical evaluation
  - Mean Tegner 6.3 → 8.3 at two years ($p<0.001$)
  - Modified Cincinnati 2.0 → 9.8 ($p<0.001$)
  - Lysholm score and Brittberg VAS showed significant improvement at 2 years ($p<0.001$)

Peterson L, Minas T, Brittberg M, et al. Treatment of osteochondritis dissecans of the knee with autologous chondrocyte transplantation: results at two to ten years. *J Bone Joint Surg Am.* 2003; 85-A (suppl 2):17-24.

MACI Sandwich Technique

Vijayan S, Bartlett W, Bentley G, et al. *J Bone Joint Surg Br.* 2012;94(4):488-492.

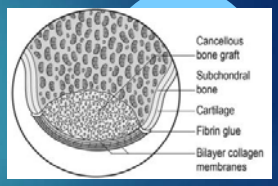
- Retrospective study
- 14 patients with a mean follow-up of 5.2 years
- Medial (10) and lateral (4) condyles
- Mean defect size: 7.2cm^2
- Lesion depth: ≥8mm

Vijayan S, Bartlett W, Bentley G, et al. Autologous chondrocyte implantation for osteochondral lesions in the knee using a bilayer collagen membrane and bone graft: a two- to eight-year follow-up study. *J Bone Joint Surg Br.* 2012;94(4):

MACI Sandwich Technique

Vijayan S, Bartlett W, Bentley G, et al. *J Bone Joint Surg Br.* 2012;94(4):488-492.

- Results
  - Mean Cincinnati knee score improved from 45.1 pre-op to 82.8 at follow-up ($p < 0.05$)
  - VAS pain improved from 7.3 to 1.7 ($p < 0.05$)
  - 12/14 (85.7%) patients were considered to have good to excellent clinical outcome
  - One graft failure at 6 years



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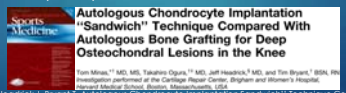
ACI Sandwich Technique

Minas et al. *Am J Sports Med.* 2017

- Cohort study; Level 3
- Two Groups
  - ACI 'Sandwich': consecutive cohort of 24 patients
    - Mean Follow-Up: 15.7 years
  - ABG: historical control group of 17 consecutive patients
    - Mean Follow-up: 7.8 years



Minas T, Ogura T, Headrick J, Bryant T. Autologous Chondrocyte Implantation Sandwich™ Technique Compared With Autologous Bone Grafting for Deep Osteochondral Lesions in the Knee. *Am J Sports Med.* 2017.

ACI Sandwich Technique

TABLE 1
Patient Characteristics[a]

	ABG (n = 13)	ACI Full Sandwich (n = 24)	P Value
Age at surgery, mean (range), y	33 (15-54)	30 (14-51)	.3943
Sex, male/female, n	8/5	13/11	.7739
Knee, right/left, n	6/7	15/9	.4991
Body mass index, mean (range), kg/m^2	26.3 (19.2-35.9)	26.3 (19.7-37.1)	.9908
Lesion type, n (%)			.8391
Osteochondritis dissecans	8 (61.5)	16 (66.7)	
Avascular necrosis	3 (23.1)	4 (16.7)	
Cyst	0 (0.0)	2 (8.3)	
Failed microfracture	2 (15.4)	2 (8.3)	

[a]ABG, autologous bone grafting; ACI, autologous chondrocyte implantation.

TABLE 2
Defect Size and Location[a]

	ABG (n = 13)	ACI Full Sandwich (n = 24)	P Value
Area, mean ± SD (range), cm^2	7.1 ± 2.7 (3-12)	6.9 ± 3.1 (3-12.5)	.6631
Depth, mean ± SD (range), cm	1.2 ± 0.4 (0.7-1.8)	1.1 ± 0.3 (0.8-1.5)	.6256
Defect location, n (%)			.3385
Medial femoral condyle	10 (77)	17 (71)	
Lateral femoral condyle	3 (23)	3 (13)	
Trochlea	0 (0)	2 (8)	
Patella	0 (0)	1 (4)	
Medial tibial plateau	0 (0)	1 (4)	

[a]ABG, autologous bone grafting; ACI, autologous chondrocyte implantation.

Minas T, Ogura T, Headrick J, Bryant T. Autologous Chondrocyte Implantation Sandwich'' Technique Compared With Autologous Bone Grafting for Deep Osteochondral Lesions in the Knee. *Am J Sports Med*. 2017.

ACI Sandwich Technique

TABLE 4
Preoperative and Postoperative Functional Scores in Patients With Retained Grafts[a]

	ABG (n = 5)			ACI Full Sandwich (n = 24)		
	Preoperative	Postoperative	P Value	Preoperative	Postoperative	P Value
Modified Cincinnati	2.6 ± 0.9	4.6 ± 2.3	.0556	3.0 ± 0.8	5.7 ± 2.0	.0001
VAS	6.4 ± 1.1	3.4 ± 0.9	.0412	6.7 ± 1.4	2.9 ± 1.6	<.0001
WOMAC total	59.0 ± 34.7	25.2 ± 21.8	.0796	48.7 ± 17.5	18.6 ± 11.1	<.0001
WOMAC pain	12.6 ± 1.5	7.4 ± 3.8	.0796	10.3 ± 3.9	3.6 ± 2.6	<.0001
WOMAC stiffness	4.6 ± 2.1	2.2 ± 1.9	.0545	4.2 ± 2.3	2.0 ± 1.2	.0012
WOMAC function	41.8 ± 5.1	15.6 ± 16.5	.0762	34.2 ± 13.6	13.0 ± 8.0	.0001
SF-36 PCS	38.2 ± 6.2	36.9 ± 3.4	.8927	37.7 ± 9.5	47.3 ± 10.5	.0004
SF-36 MCS	41.5 ± 6.9	41.1 ± 4.4	.5002	48.8 ± 6.4	54.2 ± 4.5	.0036

[a]Data are presented as mean ± SD at final follow-up. ABG, autologous bone grafting; ACI, autologous chondrocyte implantation; MCS, mental component summary; PCS, physical component summary; SF-36, Short Form-36; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Minas T, Ogura T, Headrick J, Bryant T. Autologous Chondrocyte Implantation Sandwich'' Technique Compared With Autologous Bone Grafting for Deep Osteochondral Lesions in the Knee. *Am J Sports Med*. 2017.

ACI Sandwich Technique

Higher survival rate in the "Sandwich Group"

Minas T, Ogura T, Headrick J, Bryant T. Autologous Chondrocyte Implantation Sandwich'' Technique Compared With Autologous Bone Grafting for Deep Osteochondral Lesions in the Knee. *Am J Sports Med*. 2017.

Key Points

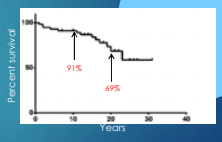
- Despite reported higher failure rates, ACI demonstrates satisfactory response rates and significant improvement in patient reported outcomes after a prior failed microfracture

Peştka JM, Bode G, Salzmann G, Südkamp NP, Niemeyer P. Clinical Outcome of Autologous Chondrocyte Implantation for Failed Microfracture Treatment of Full-Thickness Cartilage Defects of the Knee Joint. *Am J Sports Med*. 2012;40(2):325-331.

Long-Term Outcomes: Osteochondral Allograft

Raz G, et al. *J Bone Joint Surg Am*. 2014;96:1101-1107.

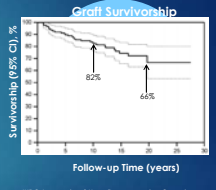
- Case series of 63 young, active patients (mean age 28 years) treated with OCA of the femur
  - Mean follow up was 21.8 years
- High rate of realignment osteotomies (62%) among patients
- Graft survival was 91% at 10 years and 69% at 20 years
- Mean modified HSS score of patients with a surviving allograft at 15 years was 86 (excellent)
- Majority of patients had a structurally intact graft that was well united to the host bone



Raz G, et al. *J Bone Joint Surg Am*. 2014;96:1101-1107.

Long-Term Outcomes: Osteochondral Allografts

- 122 patients (129 knees) underwent OAT
  - Mean age was 32.8 years
  - Median follow up of 13.5 years
    - 91% of patients had >10 years follow up
- Mean scores of all clinical outcomes significantly improved from baseline to final follow up
  - Modified d'Aubigne-Postel: 12.2 to 16.0 (*P*<0.001)
  - IKDC pain: 7.0 to 3.8 (*P*<0.001)
  - IKDC function: 3.4 to 7.2 (*P*<0.001)
  - Knee Society function: 65.6 to 82.5 (*P*=0.005)
- Graft survival was 66% at 20 years (Figure)
- Age of ≥30 years and ≥2 previous surgeries were significantly associated with osteochondral allograft failure (*P*<0.05)

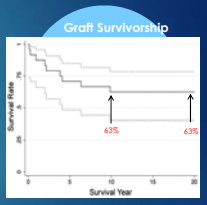


IKDC: International Knee Documentation Committee; OAT: osteochondral allograft transplantation surgery.

Levy YD, et al. Do fresh osteochondral allografts successfully treat femoral condyle lesions? *Clin Orthop Relat Res*. 2013;471:231-237.

Long-Term Outcomes First Generation ACI

- 23 patients (24 knees) underwent first-generation ACI
  - Mean Age 35.4 years
  - Median follow-up 20.6 ± 0.3
  - Total defect area: 11.8 ± 8.0
- Mean scores of clinical outcomes significantly improved from baseline to final follow up
  - Mean Modified Cincinnati: (P < .01)
  - Mean VAS: (P < .001)
  - Mean WOMAC: (P < .001)
  - Mean SF-36 PCS (P < .001)
- Graft Survival was 63% at 20 years
- All patients with retained grafts over 20 years were satisfied with ACI



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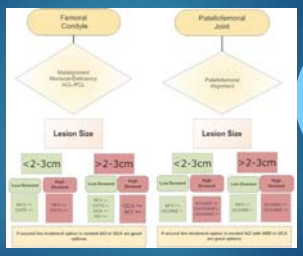
Cartilage Treatment Algorithm



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Thank You

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