Articular Cartilage Repair and Restoration

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I (and/or my co-authors) have something to disclose.

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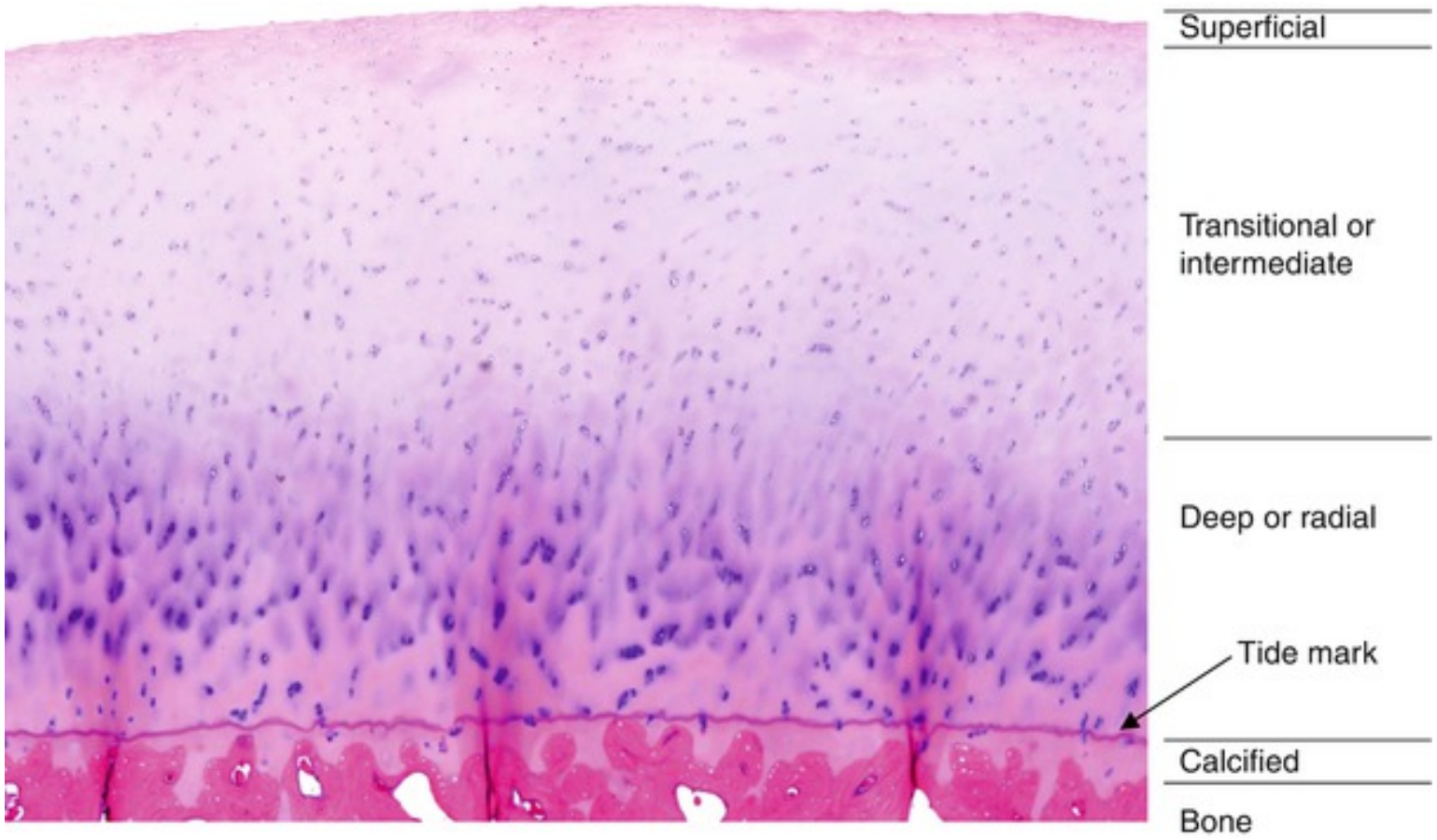
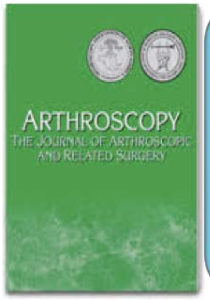
Articular Cartilage



Cartilage Pathology → Common!

Articular Cartilage Defects in 1,000 Knee Arthroscopies

Karin Hjelle, M.D., Eirik Solheim, M.D., Ph.D., Torbjørn Strand, M.D., Rune Muri, M.D., and Mats Brittberg, M.D., Ph.D.



61%

Articular cartilage defects: Study of 25,124 knee arthroscopies

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60%

Articular Cartilage Lesions in 993 Consecutive Knee Arthroscopies

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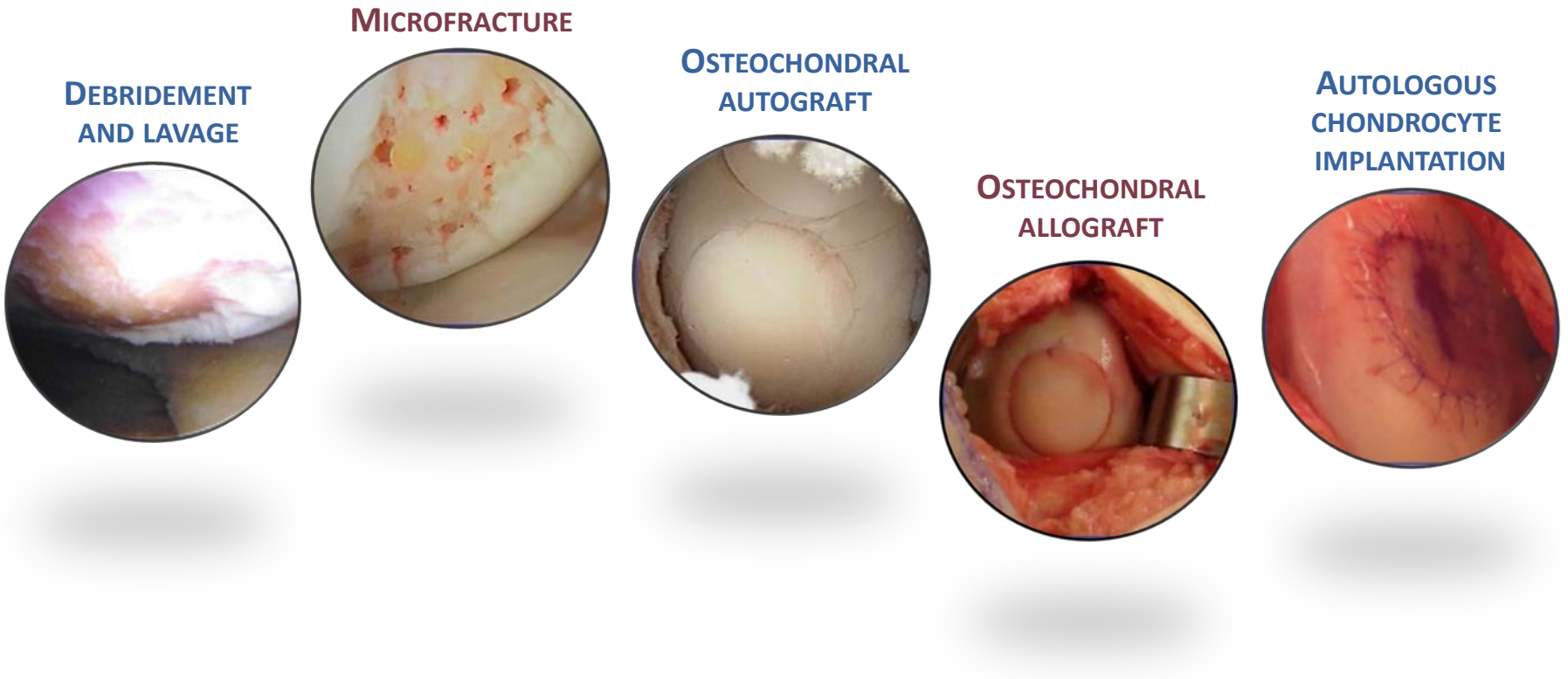
From the †Oslo Sports Trauma Research Center, ‡Institute for Surgical Research, §Akershus University Hospital, ‖Oslo University Orthopaedic Clinic, and [a]Martina Hansen Hospital.

66%

Outerbridge Arthroscopic Grading System	
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 1.5 cm in n diameter)
Grade III	Deep fissures at the level of subchondral bone with a diameter more than 1.5 cm
Grade IV	Exposed subchondral bone

ICRS (International Cartilage Repair Society) Grading System	
Grade 0	Normal cartilage
Grade 1	Nearly normal (superficial lesions)
Grade 2	Abnormal (lesions extend < 50% of cartilage depth)
Grade 3	Severely abnormal (>50% of cartilage depth)
Grade 4	Severely abnormal (through the subchondral bone)

Many Options Are Available for Treating Focal Cartilage Defects that are Symptomatic



Bentley G, et al. *Injury*. 2013;44(Suppl1):S3-S10. Image of debridement courtesy of Dr. Brian Cole; images of microfracture, osteochondral autograft, and osteochondral allogaft courtesy of Dr. Christian Lattermann; image of autologous chondrocyte implantation courtesy of Dr. Jack Farr.

Courtesy Peter Bak

Currently available for general use

- Palliative: Debridement (chondroplasty)
- Reparative: Marrow Stimulation & Augments
- Restorative: Cell therapy; Osteochondral Auto and Allografts

Why Not More Options?
Barriers in Pathway to the Market

human cells, tissues, cellular and tissue-based products

HCT/P 351 requires RCT for biologic license

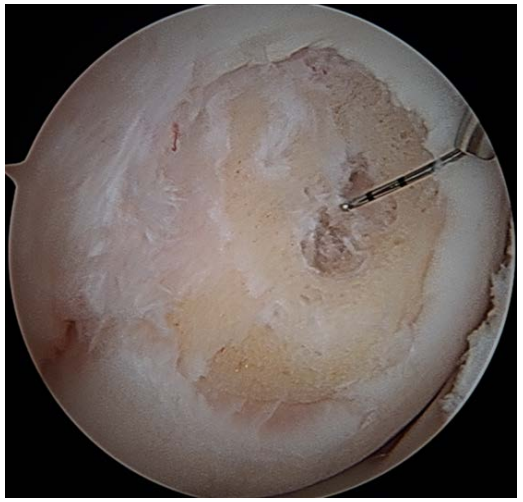
- manipulation
- culturing
- addition of growth factors
- non-homologous use

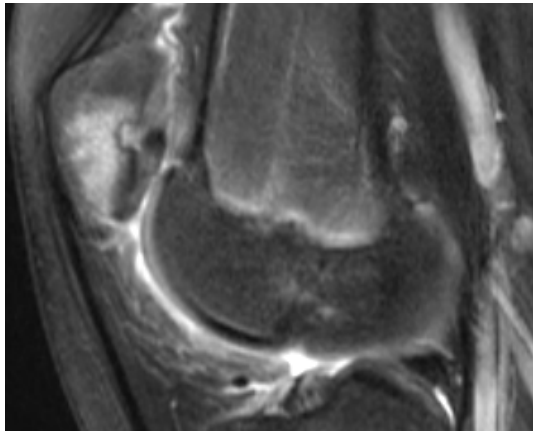
RCT

- typical 200-300 subjects
- enrollment difficult 2° exclusion criteria
- 2 years from pilot to pivotal; 2 yr enrollment; 2 yr follow-up 1-2 yr data analysis and submission
- expense range of $10-30,000,000

The Cartilage Lesion

- Size
- Contained /uncontained
- Bone loss
- Bone marginal viability (OD/AVN)
- Sub-adjacent bone marrow lesions
- Adjacent chondropenia



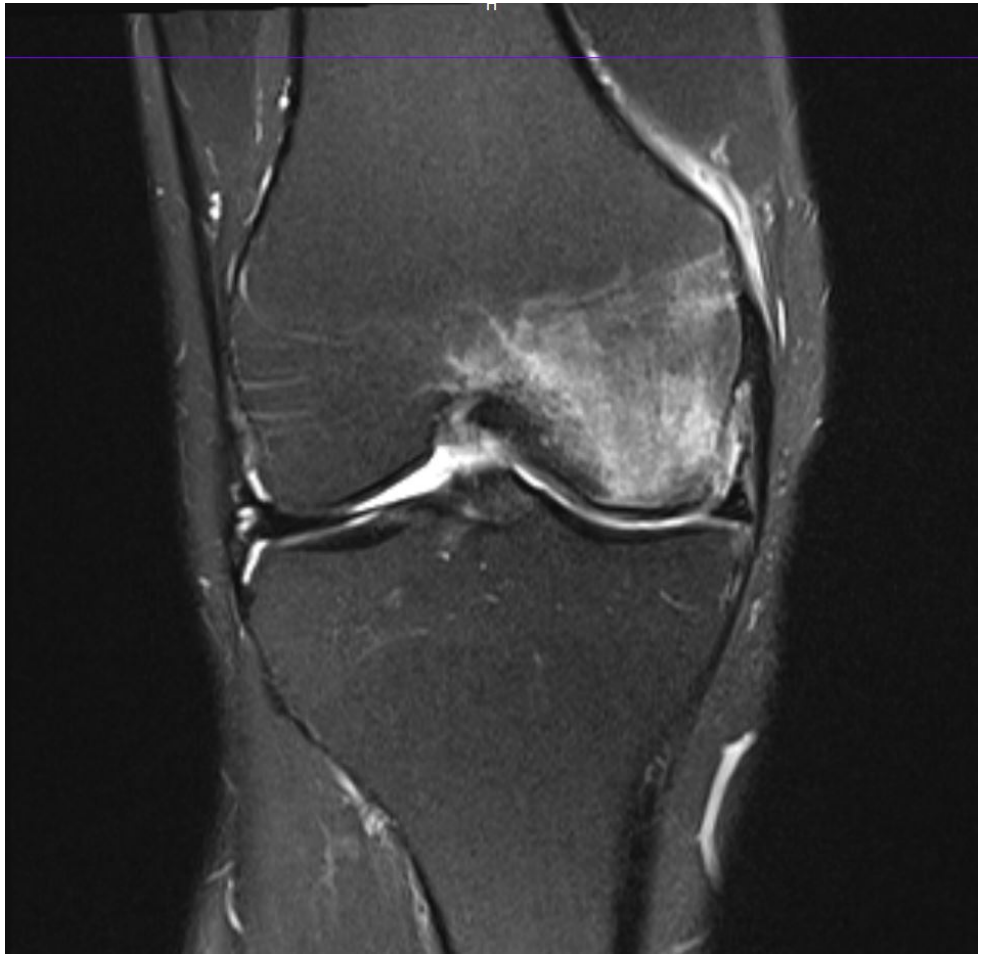


The Patient

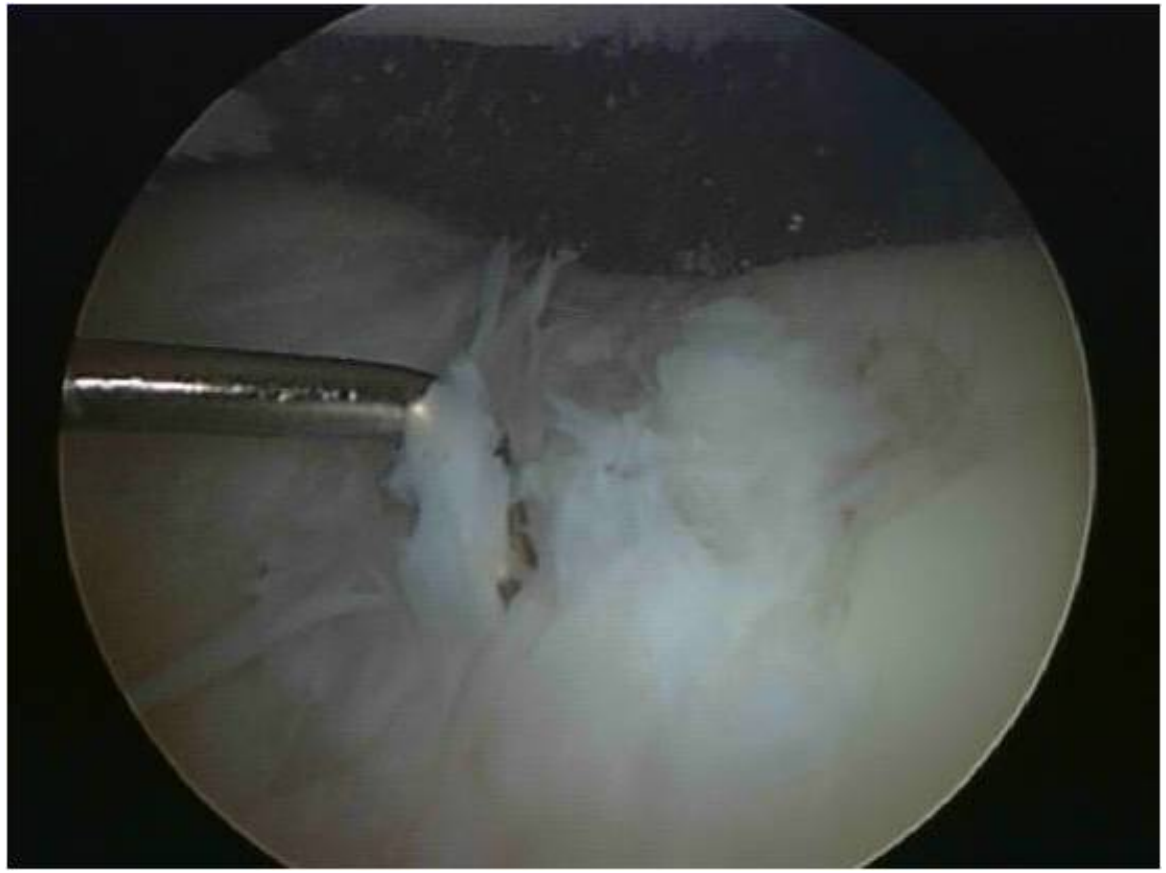
- systemic illnesses (inflammatory)
- age
- mental outlook (depression/ unrealistic expectations)
- obesity
- genetic predisposition to OA

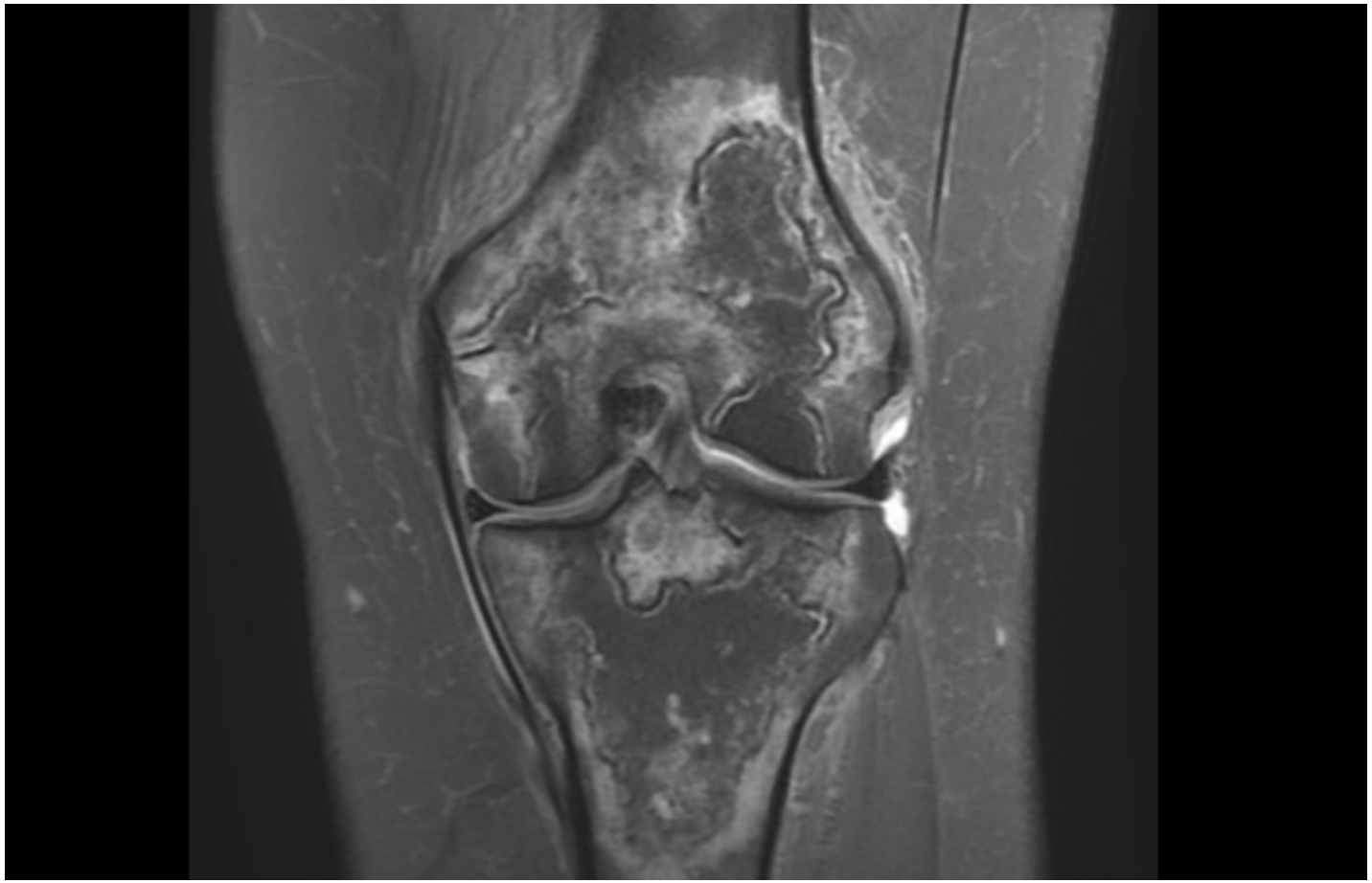
Still playing pro basketball 9 years later

Address the source of the problem



Always look beyond the surface



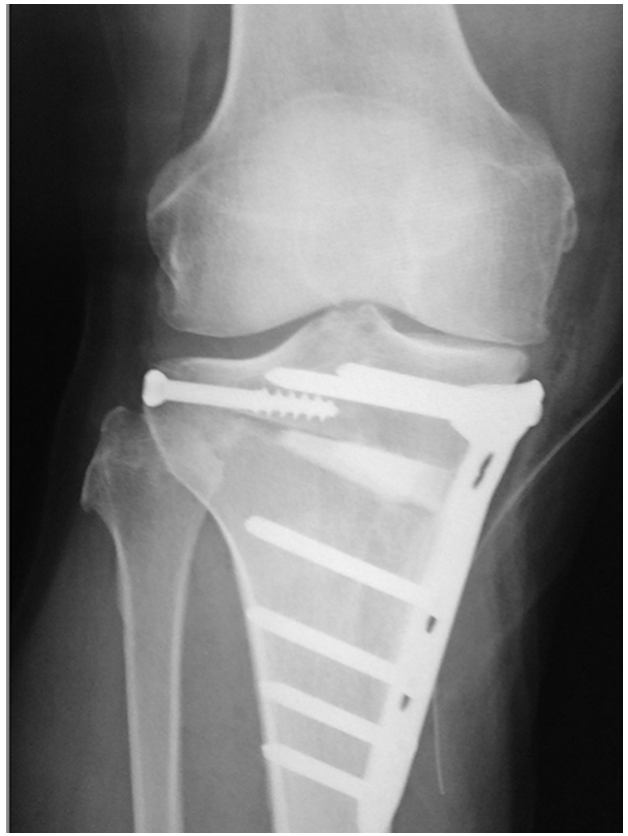


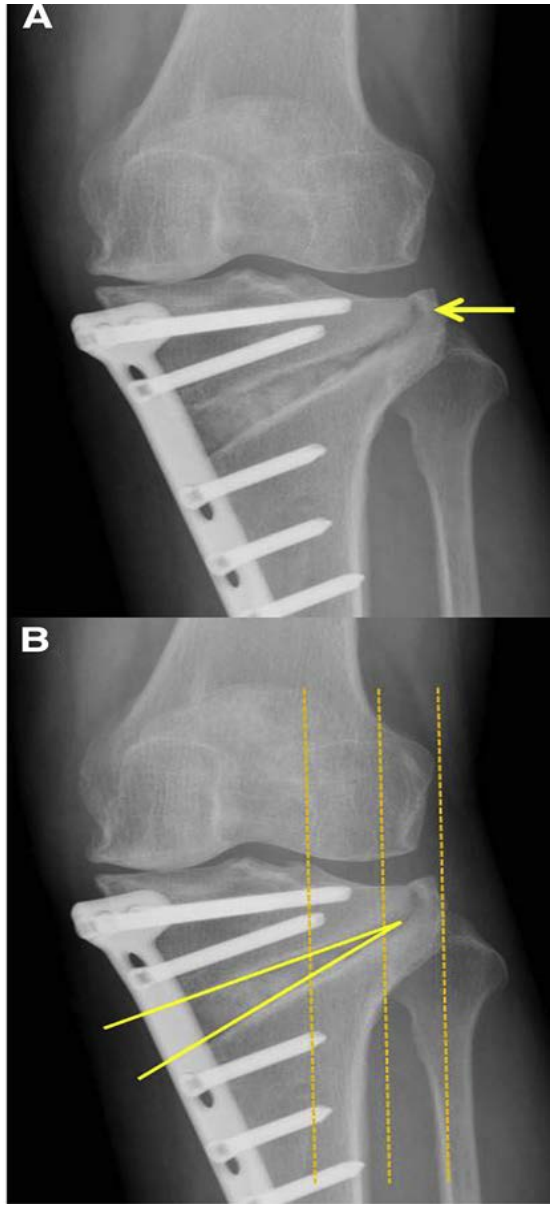
Co-Morbidities

- The knee beyond the lesion
- The patient
- The limb
- Other joints


UPRIGHT
cm

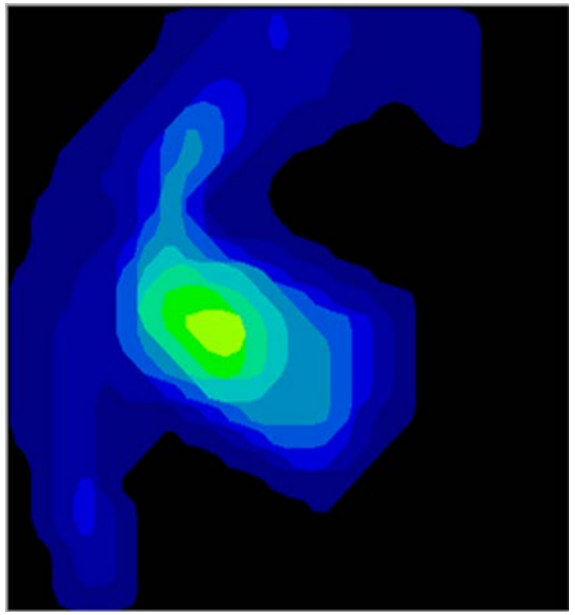
Simple procedure?



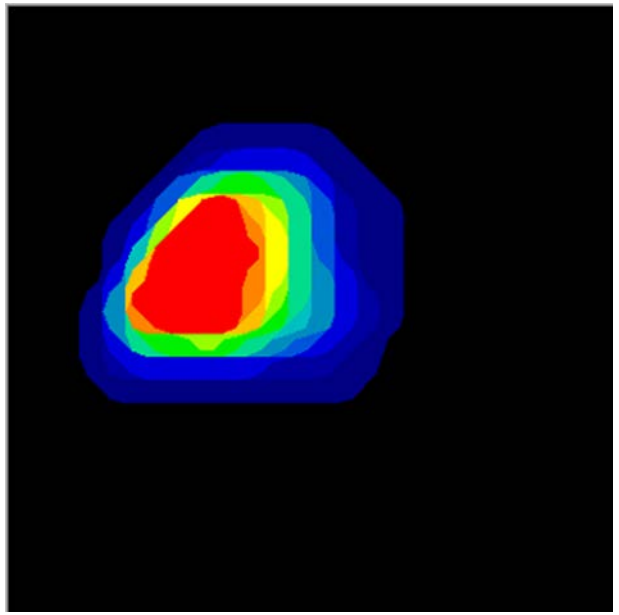


Son et al. Arthroscopy 11/2021

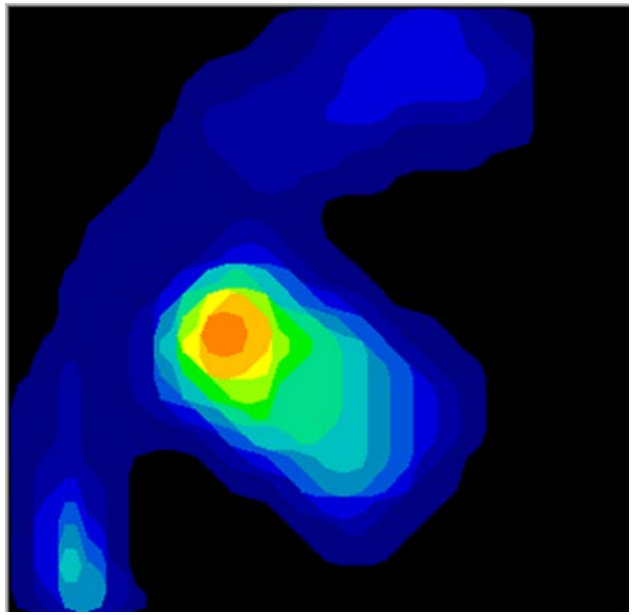
Biomechanically- Medial MAT improves stress distribution



Normal

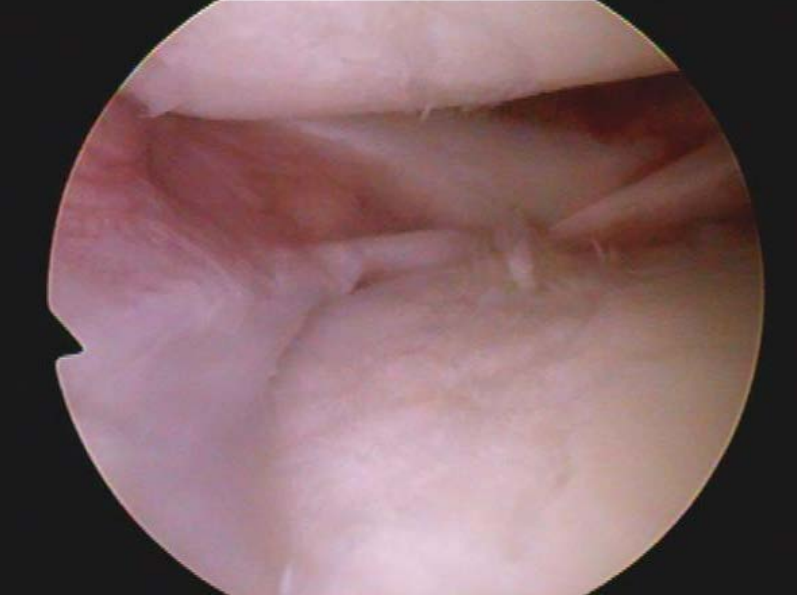


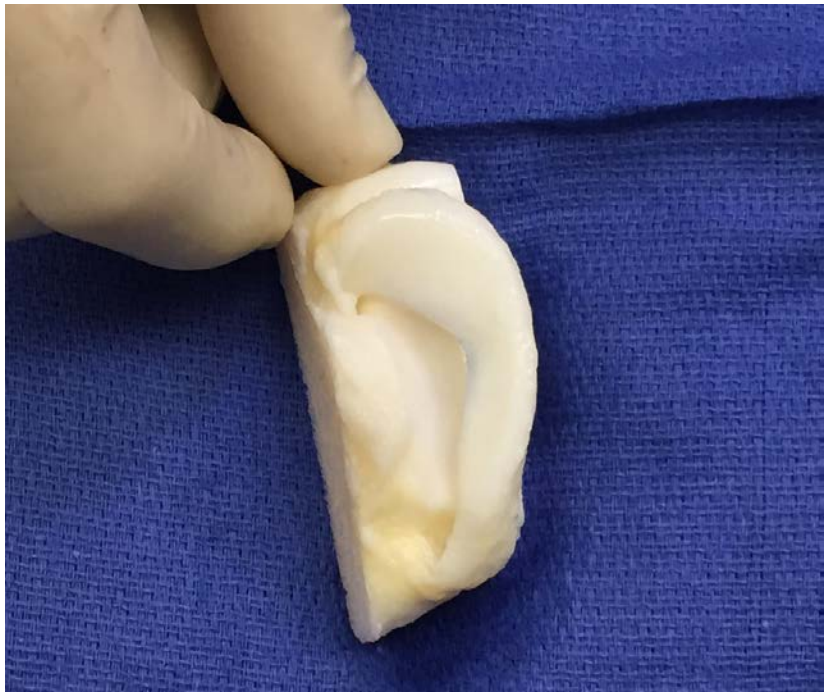
Meniscectomy

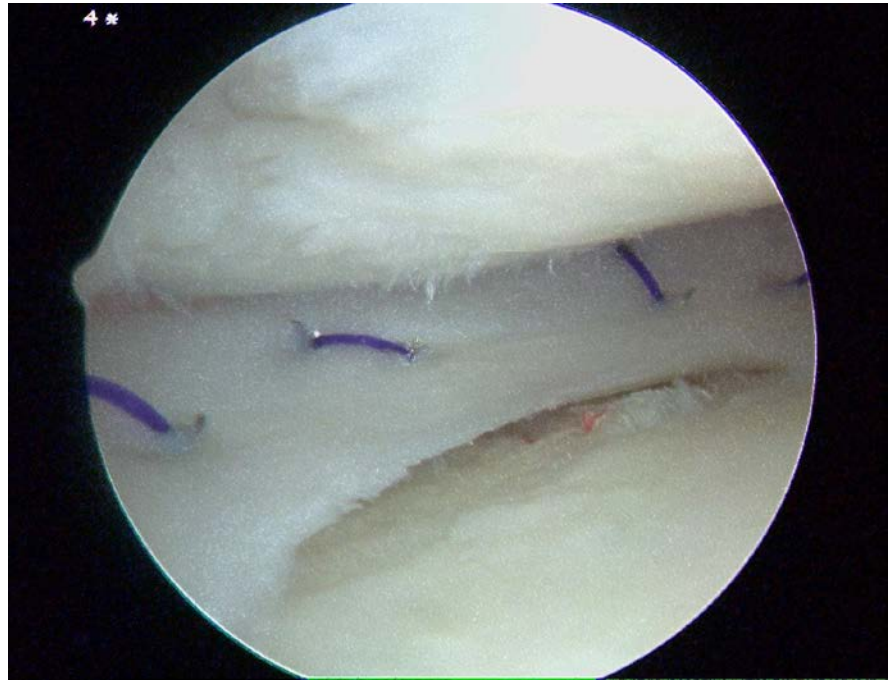


Meniscal Allograft

Courtesy Farr and Verma



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Meniscal Allograft Survivorship and Outcomes 20 Years After Implantation

Carter and Brown

Arthroscopy 2020;36:2268-2274

- 48 of initial 56 recipients (85.7%)
- 27/48 patients had no additional surgeries- graft survivorship of 56.2% at 20 years
- 8 had knee arthroplasty

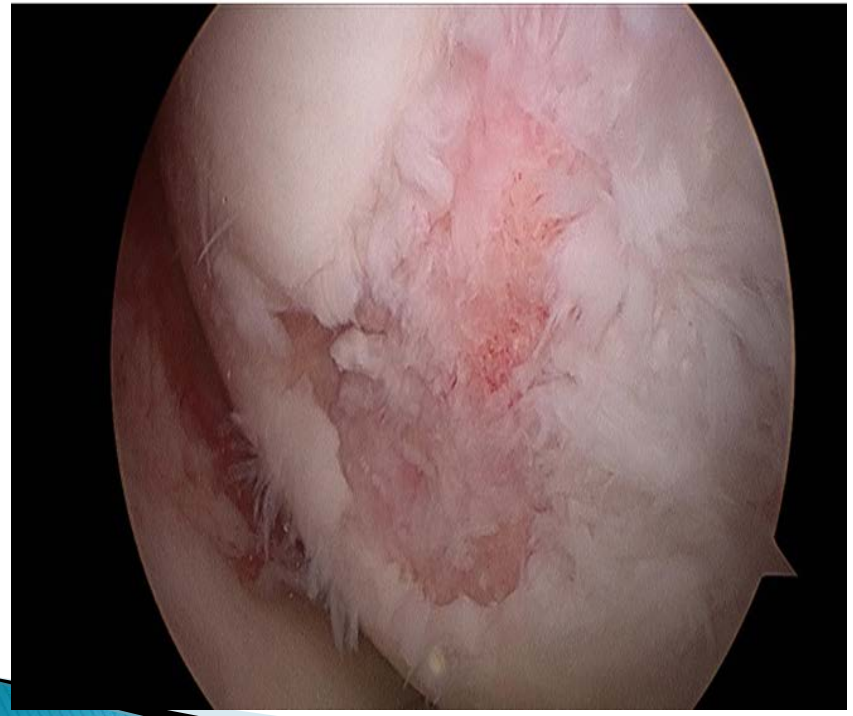
  -average 14 year post-op

Chondroplasty

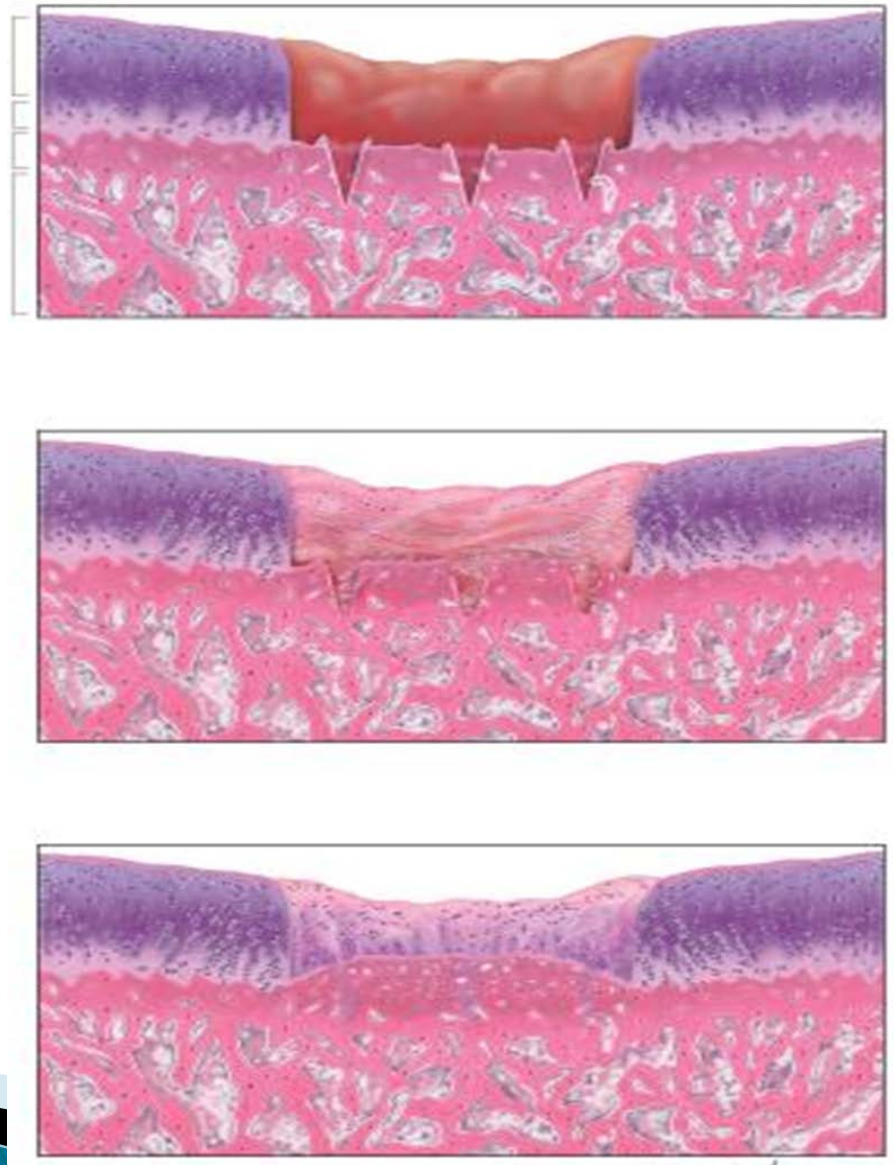
- can be useful but often abused
- mechanical symptoms and swelling have best success
- benefit often short term

Microfracture

pluripotential marrow (MSC) cells
create fibrocartilage



Drill Don’t Pick!



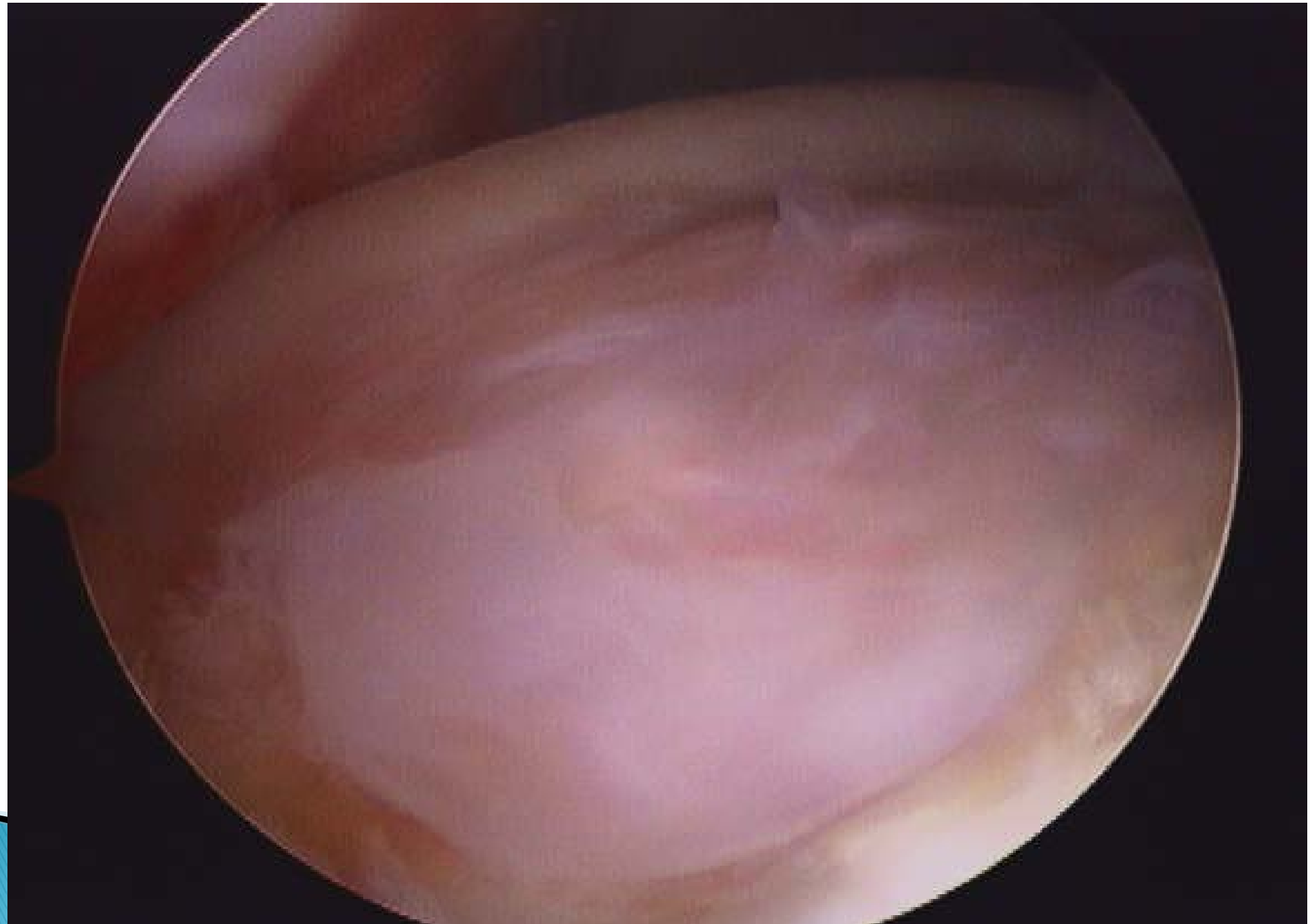
Clinical efficacy of MF-evidence based systematic analysis

Mithoefer et al. Am J Sports Med 2009: 2053-62

- 28 studies
- 3122 patients
- improvement
  - -75-100% at 2 years
  - -67-86% 5 years

Factors Affecting Outcome

variable	better outcome
age	<40 yrs
lesion size	<4 cm^2
	athletes<2 cm
duration	<12 months
BMI	<30
fill volume	>66%



Biocartilage

Micronized Cartilage Matrix

- Dehydrated allograft cartilage
- Micronized (ground) to small particle size to increase S.A.
- Retention of:
  - ✓ ECM: Type II collagen, Aggrecan, Decorin
  - ✓ GF: TGF, FGF, PDGF, VEGF, BMP-7, EGF, IGF,etc

BioCartilage

Components

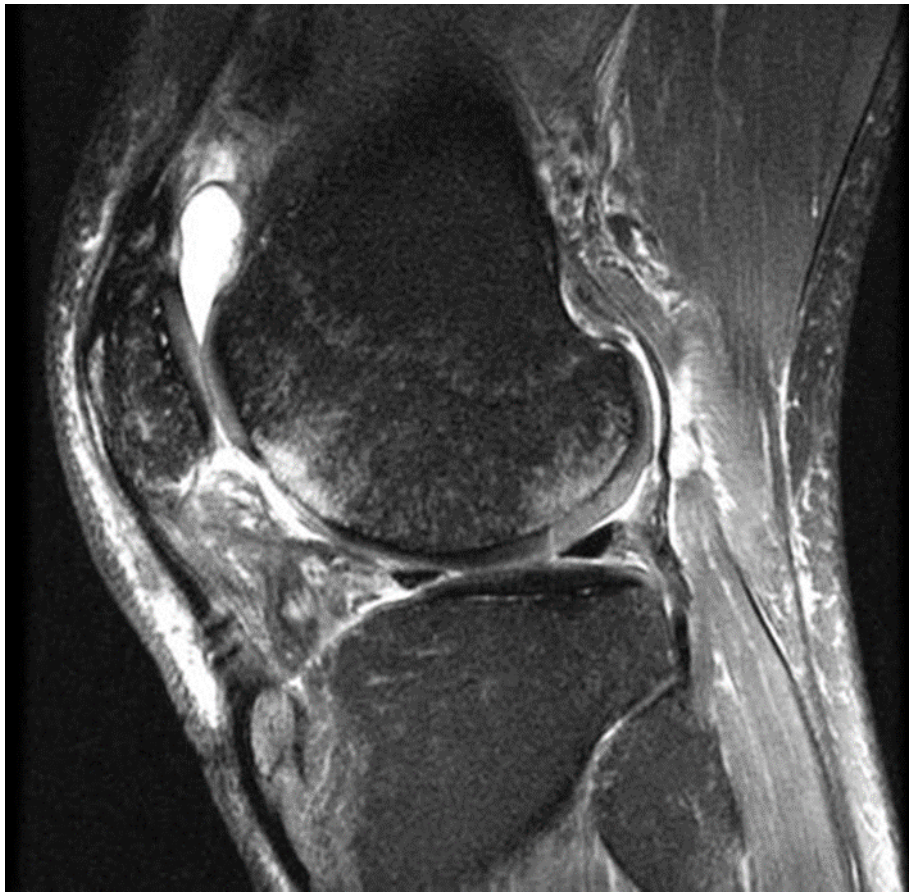
- 1.0 cc of BioCartilage
- 1.0 cc of PRP
- Mixing syringe and applicator
- Fibrin Glue
- “Atraumatic” Microfracture

Clinically Significant Outcomes Following the Treatment of Focal Cartilage Defect of the Knee with Microfracture Augmentation Using Cartilage Allograft Extracellular Matrix

Cole, Haunschild, Carter, et al. Arthroscopy 2021;37:1512-1521

Conclusions

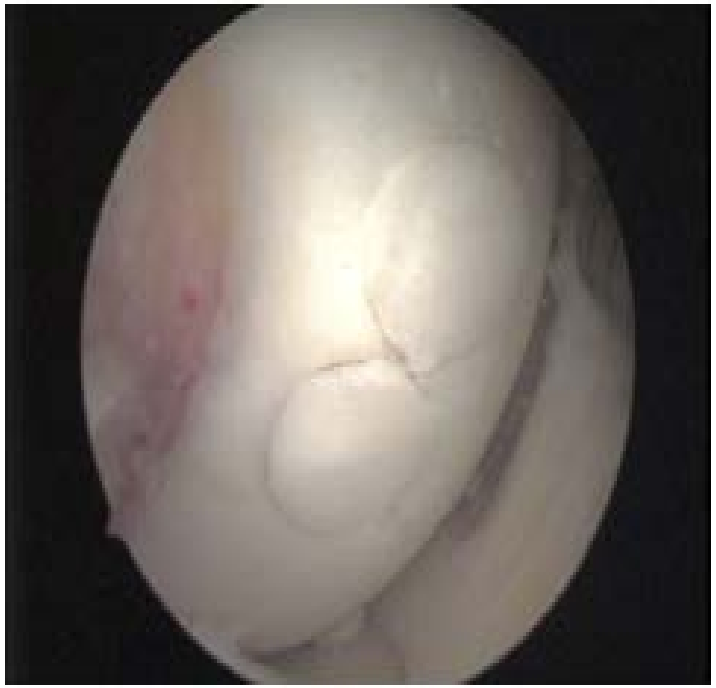
In this preliminary study, we found cartilage allograft extracellular matrix to be associated with a significant improvement in functional outcomes, high rates of CSO achievement, and low failure and complication rates at 2-year follow-up.

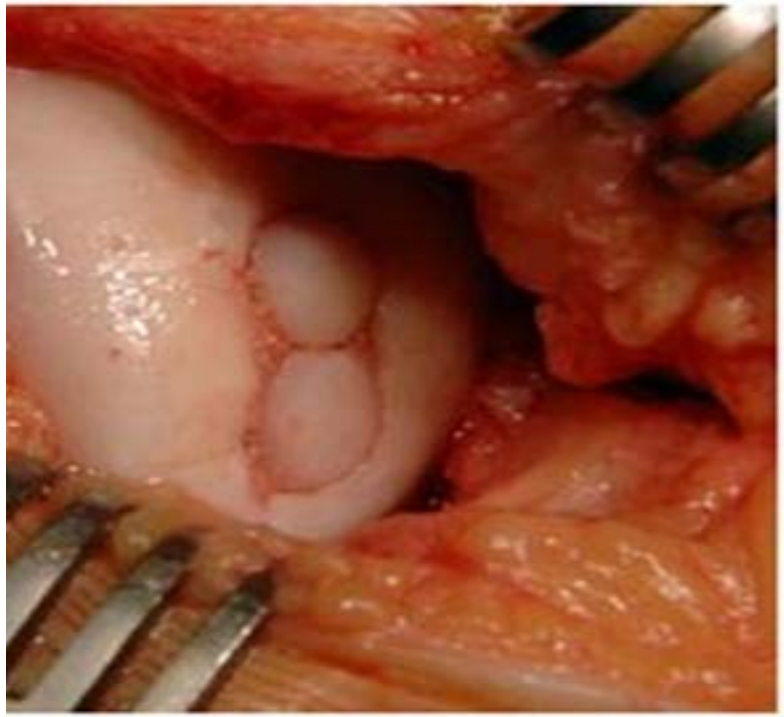


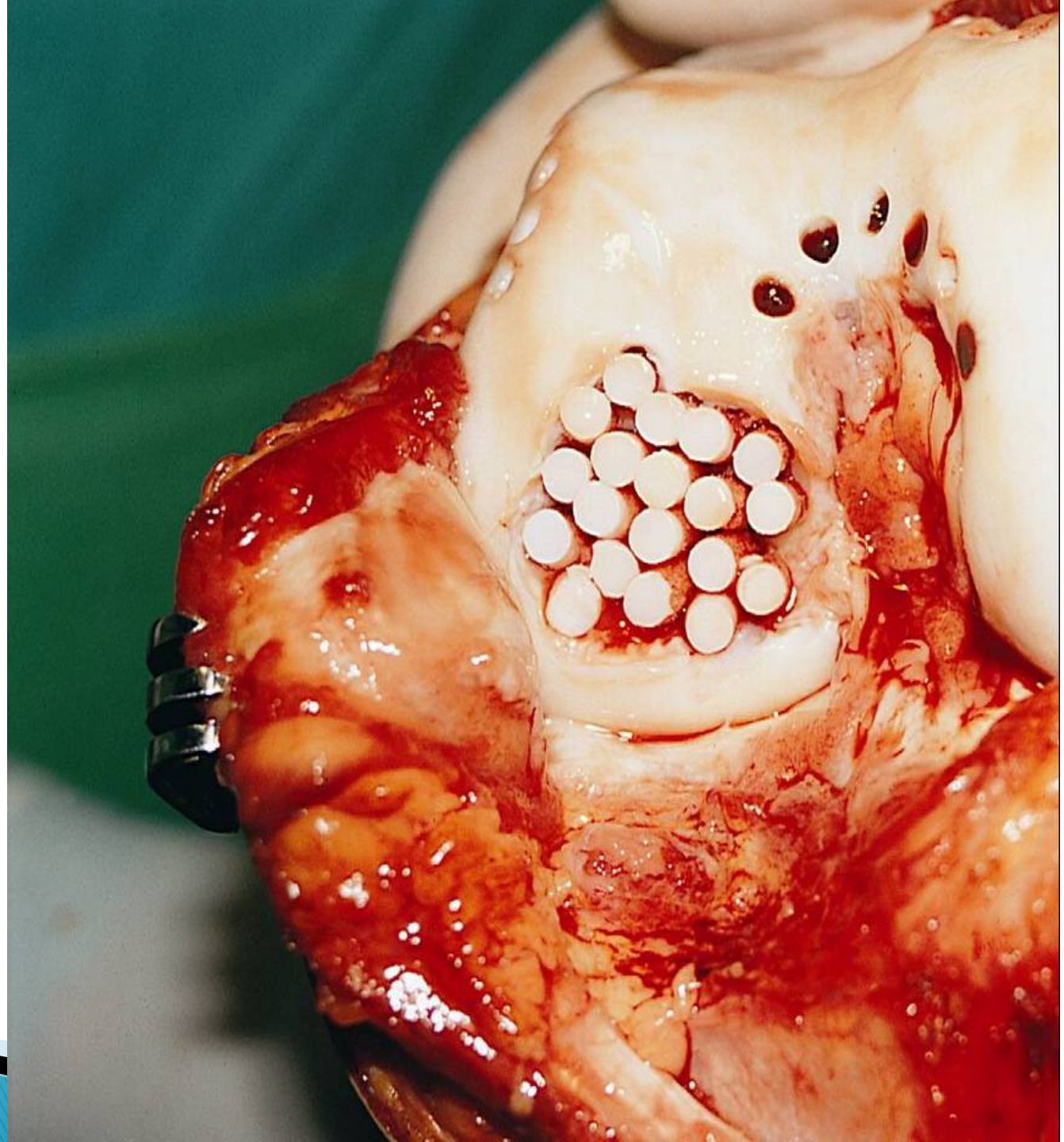
OATS

osteochondral autograft transfer

cylindrical plug of healthy articular cartilage and bone is transferred to one with an articular cartilage defect



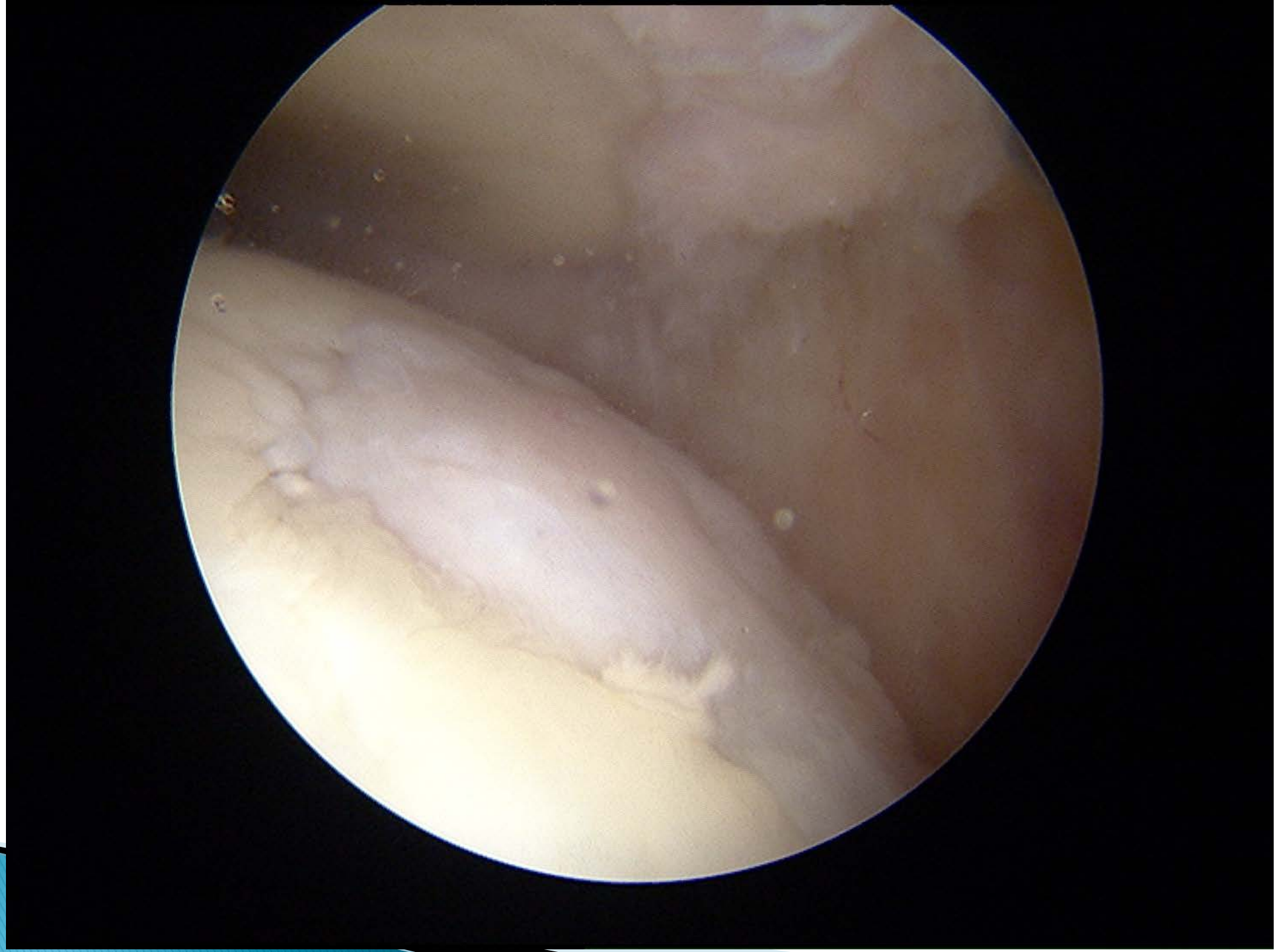




Long-term Outcomes After Osteochondral Autograft Transfer:A Systematic Review Mean 10.2 Years F/U

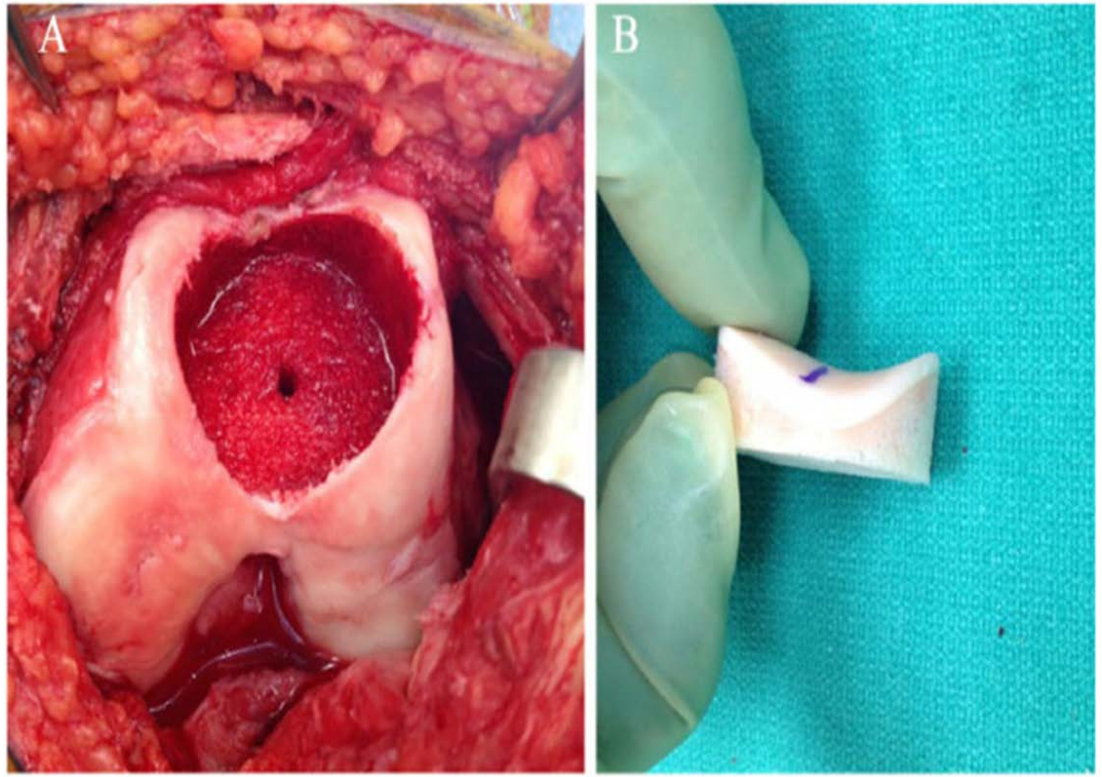
Pareek et al. Arthroscopy . 2016;32:1174-1184

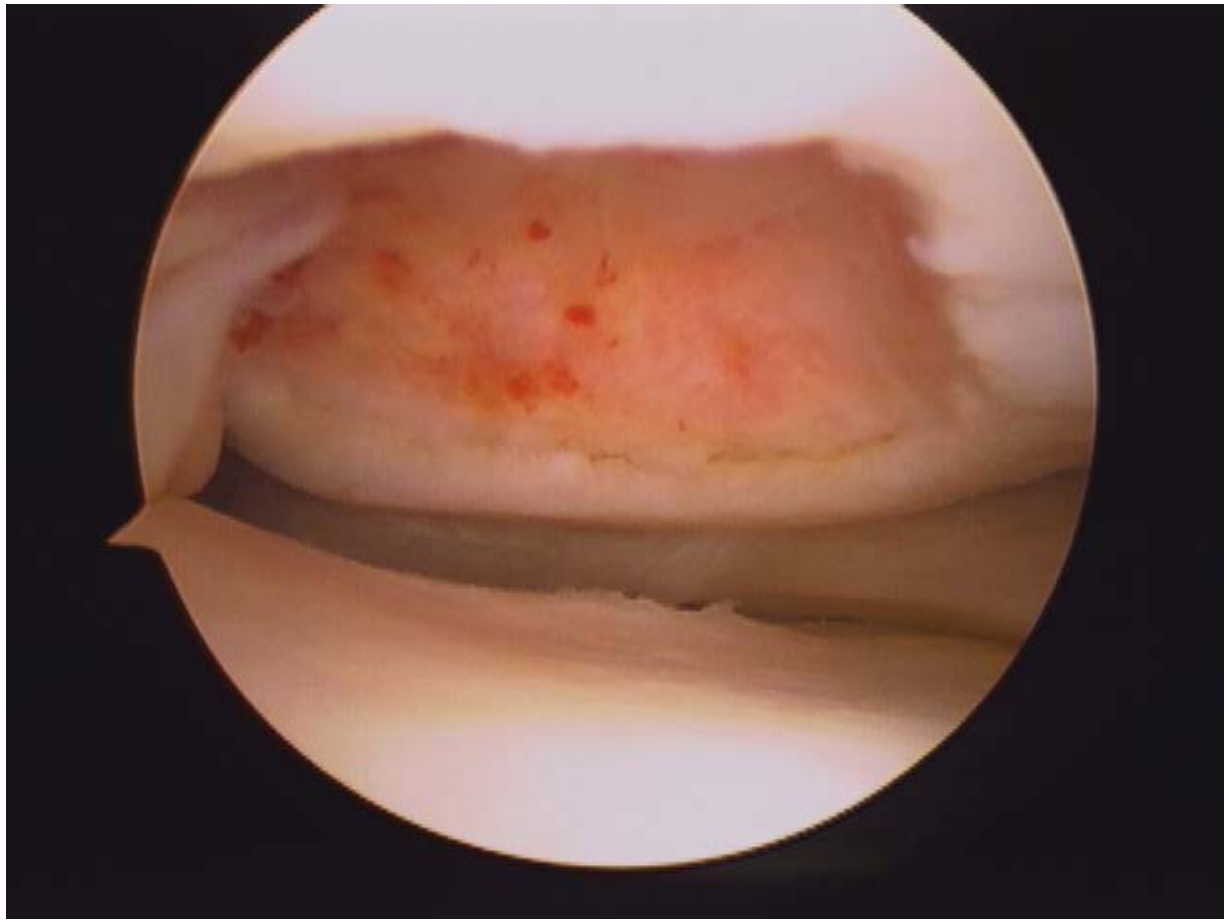
- 610 patients-10 studies
- Average age 27.0 yrs
- Lesion size ave 2.6 cm^2 (.9-20cm)
- Mean follow-up 10.2 yrs (9-17.5 yrs)
- Successful outcome 72%
- Reoperation rate 19%



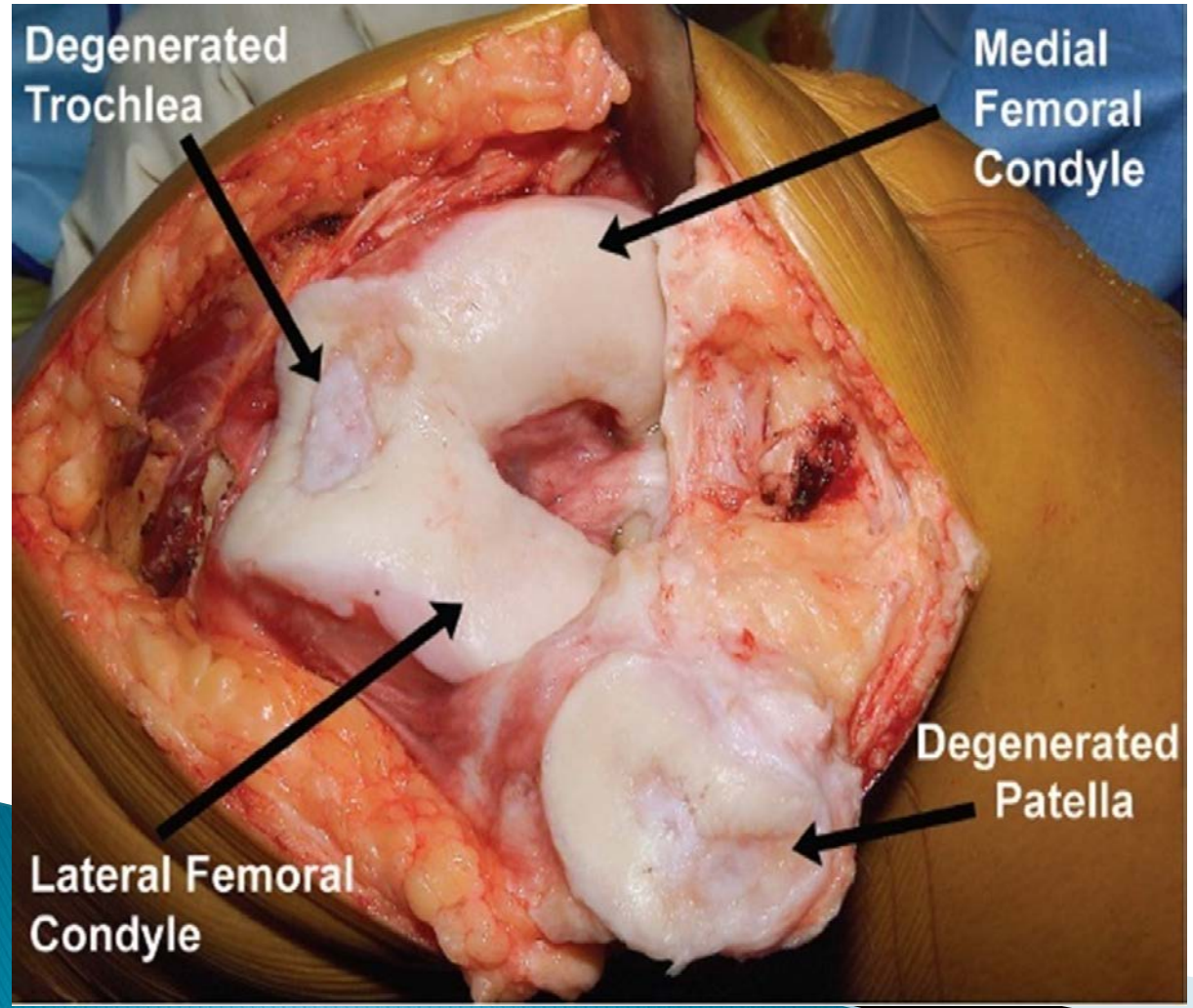
Osteochondral allografts

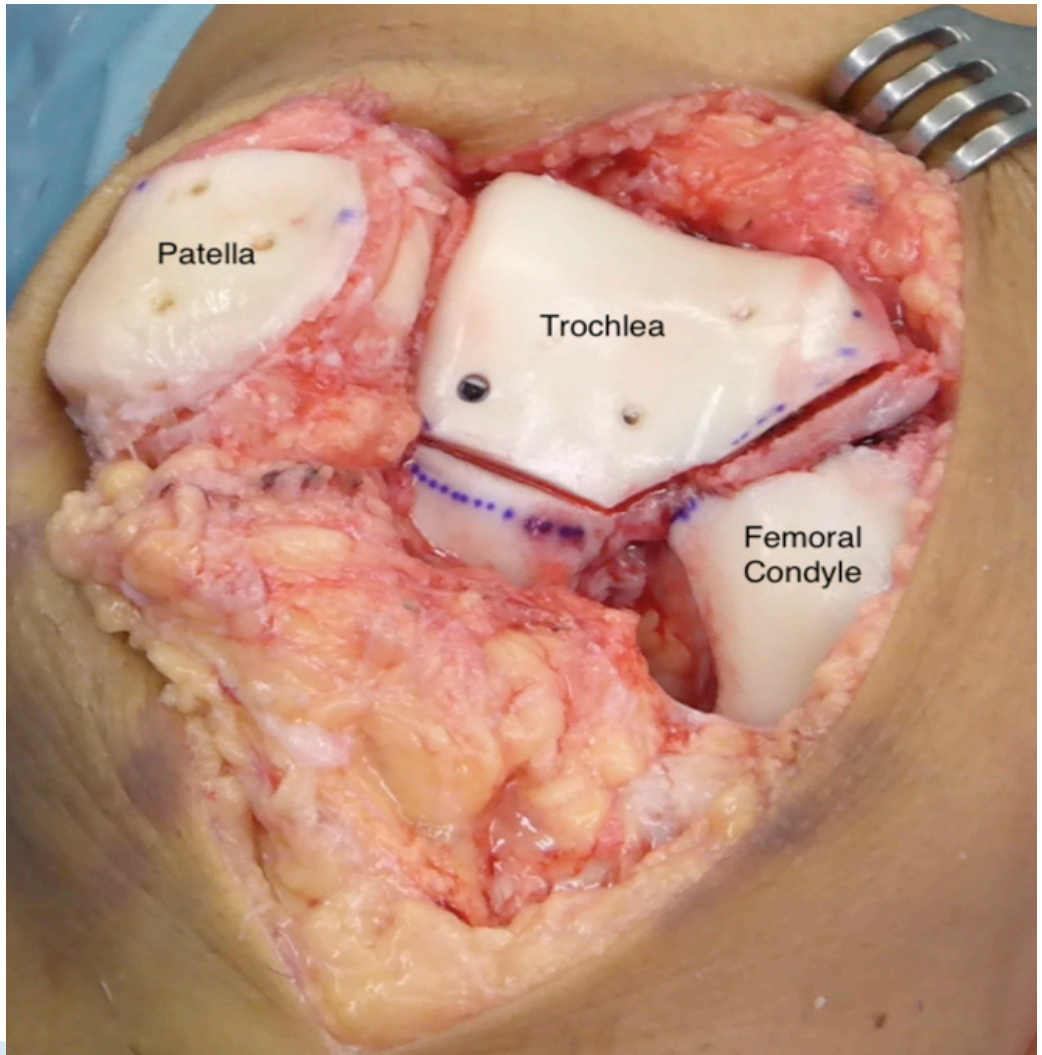
- Larger lesions
- Bone and cartilage involvement
- Salvage
- Issues of availability
- Issues of optimal storage
- Issue of precise fit/chondrocyte death





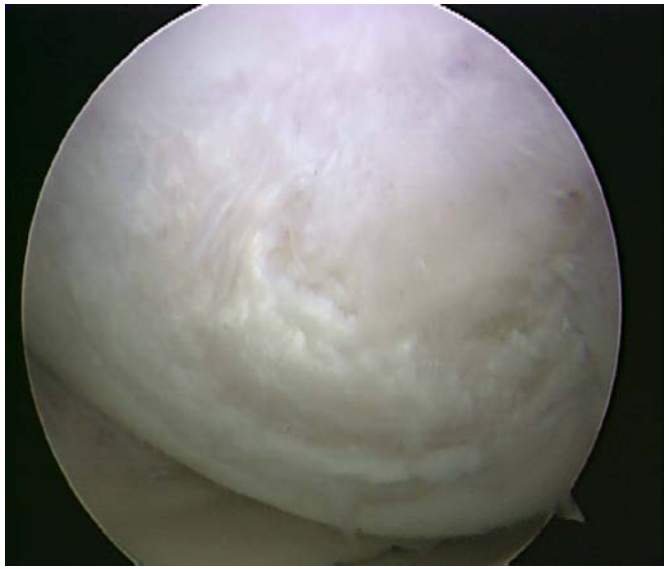
Osteochondral Allograft
No Limit of Shape, Size or Thickness





Only Fresh Grafts

- frozen have no viable cells
- cells required to maintain matrix
- 70% cell survival at 28 days
- 14 days required for infectious disease testing
- upper age limit of donor 40 years old



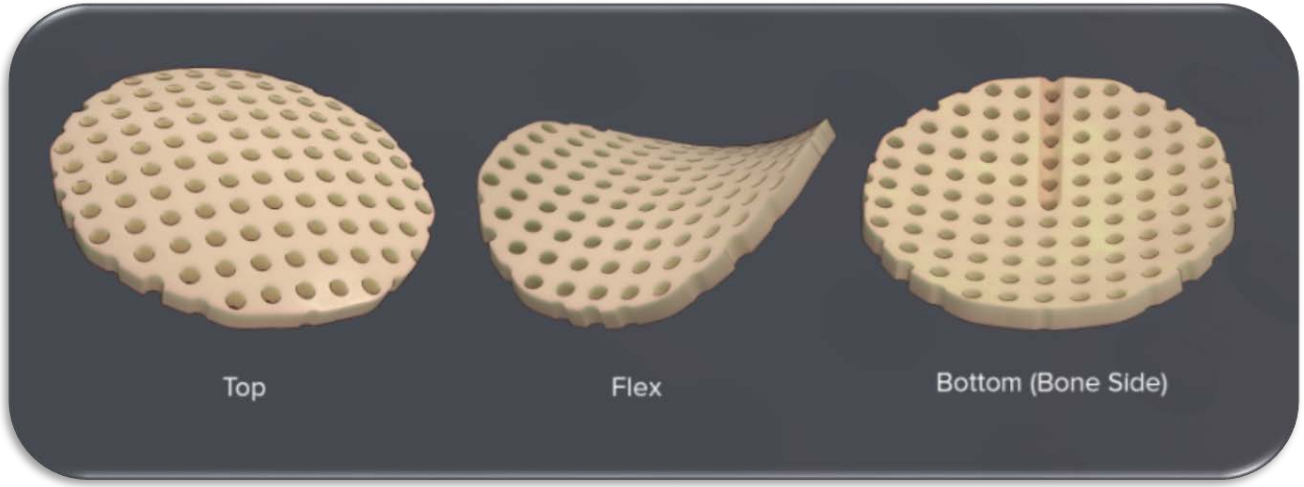
Clinical Outcomes and Failure Rates of Osteochondral Allograft Transplantation in the Knee: a Systematic Review Familiari et al. Am J Sports Med 2018;46:3541-3549

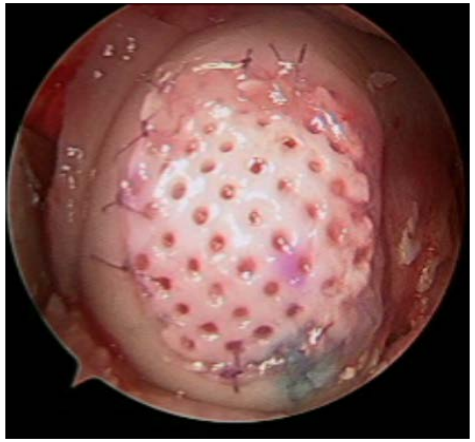
- 1036 patients
- mean 5 yrs follow-up 86.7%
- mean 10 yrs 78.7%
- mean 15 yrs 72.8%
- mean 20 yrs 67.5%
- Revision, patella and bipolar lesions lower survival
  -Gracitelli et al. 78.1% patella at 5 yrs

Technical Pearls

- the graft should have only enough bone to enable healing to the host (total thickness of 6-8mm)
- augment fixation if dowel graft not at least 80% contained
- insert graft with gentle pressure (force kills the chondrocytes)

Cartiform (osteochondral allograft)





Osteochondral Allografts

- Time tested
- Articular cartilage- not hyaline like or fibrocartilage
- No limit of shape, size, or thickness
- Rejection/infection- negligible with proper screening and procurement

Autologous Chondrocyte Implantation
ACI 1st generation

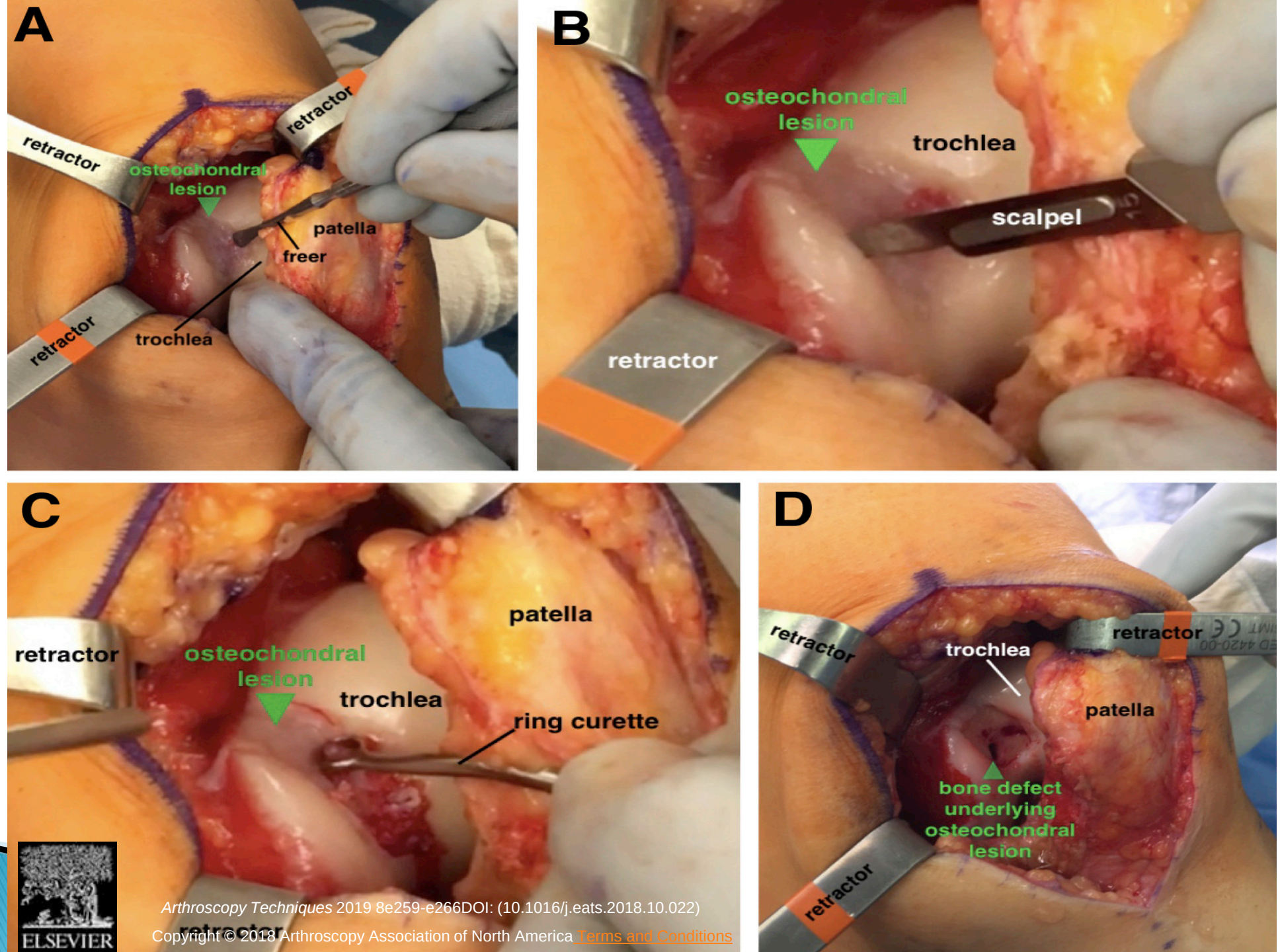
Biopsy

↓

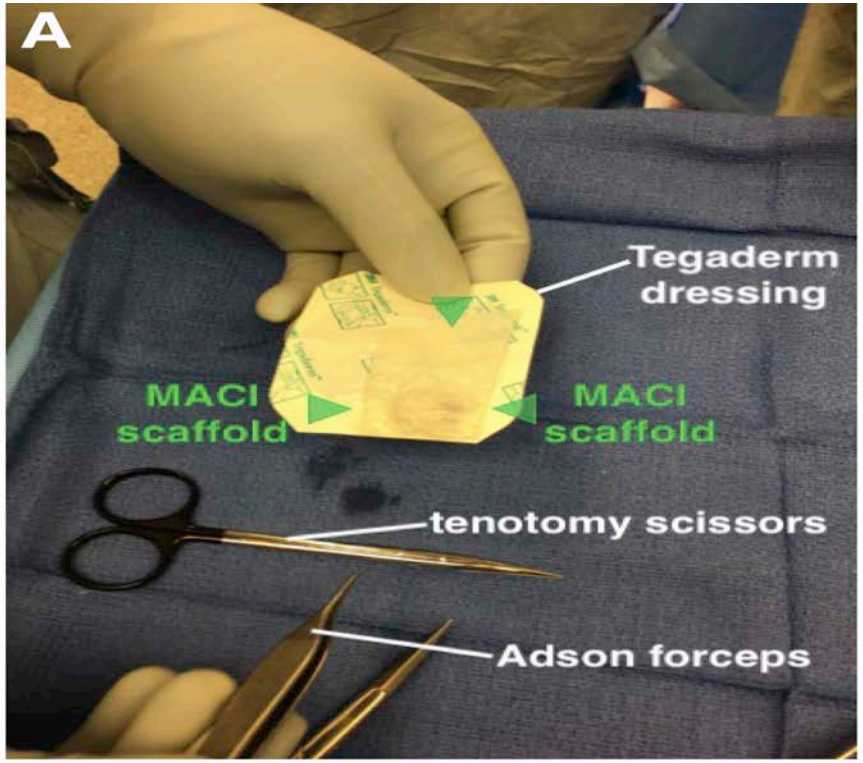
Culture

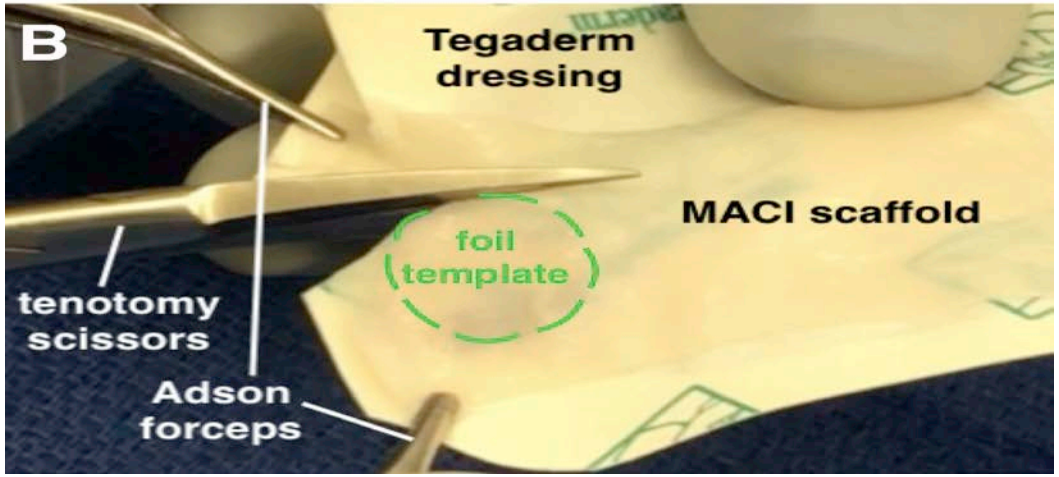
↓

Implantation

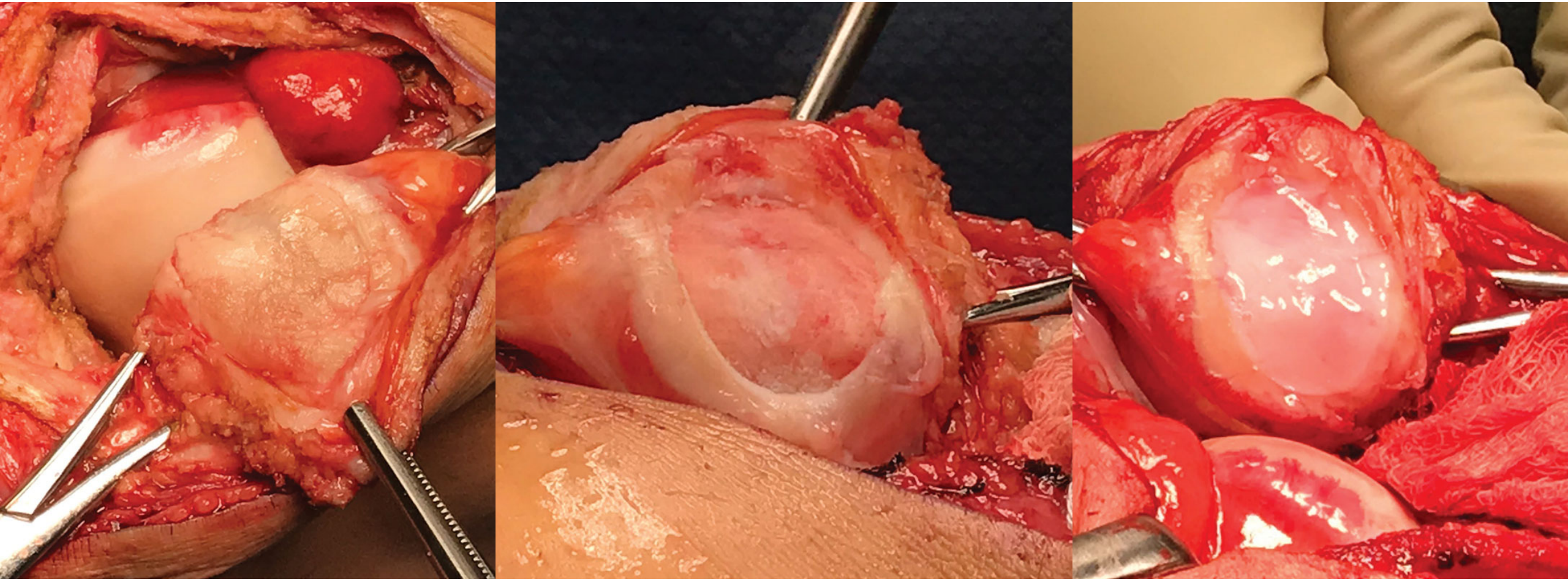


Arthroscopy Techniques 2019 8e259-e266DOI: (10.1016/j.eats.2018.10.022)





Arthroscopy Techniques 2019 8e259-e266DOI: (10.1016/j.



Minimum 10-year outcome study of ACI

Minas et al. Clin Orthop Relat Res 2014;472:41-51

- 210 patients
- mean 12 +/-2 years
- mean defect size 8.4 cm^2
- 71% survivorship
- 75% improved function

ACI (MACI)

Pros

- potential for treating large lesions
- 20 year track record

Cons

- 2 operations
- expensive
- “hyaline-like” cartilage

Treatment Algorithm

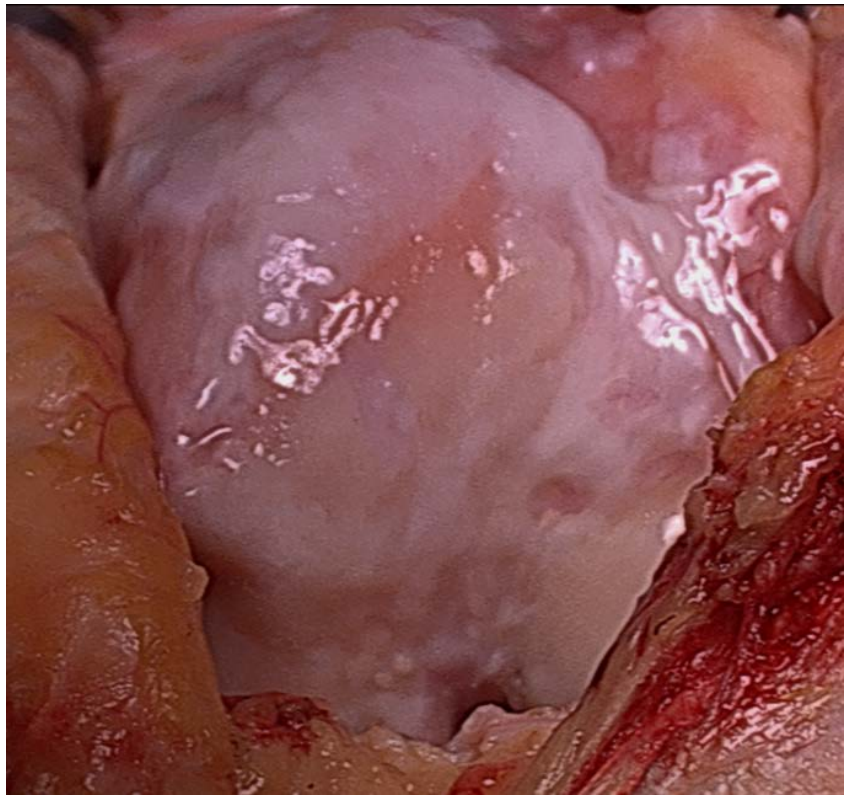
Lesion size

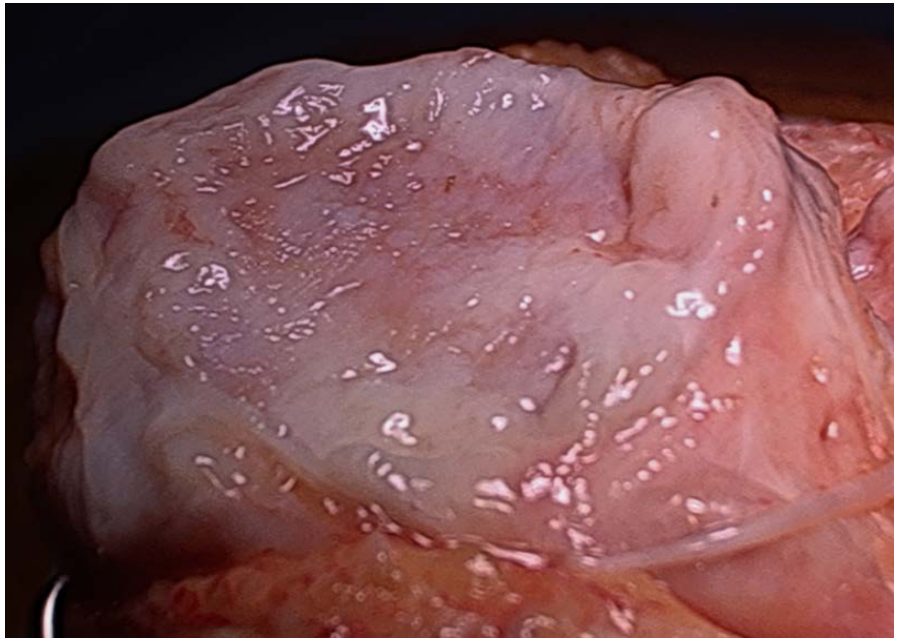
		< 2–2.5cm²	≥ 2–2.5 cm²
1º	Microfracture / Biocartilage	+/+	+/–
	OC Autograft	+/+	+/–
	ACI		+/+
	OC Allograft		+/+
2º	OC Autograft	+/+	
	ACI	+/–	+/+
	OC Allograft	+/–	+/+

Conclusions (for all methods)

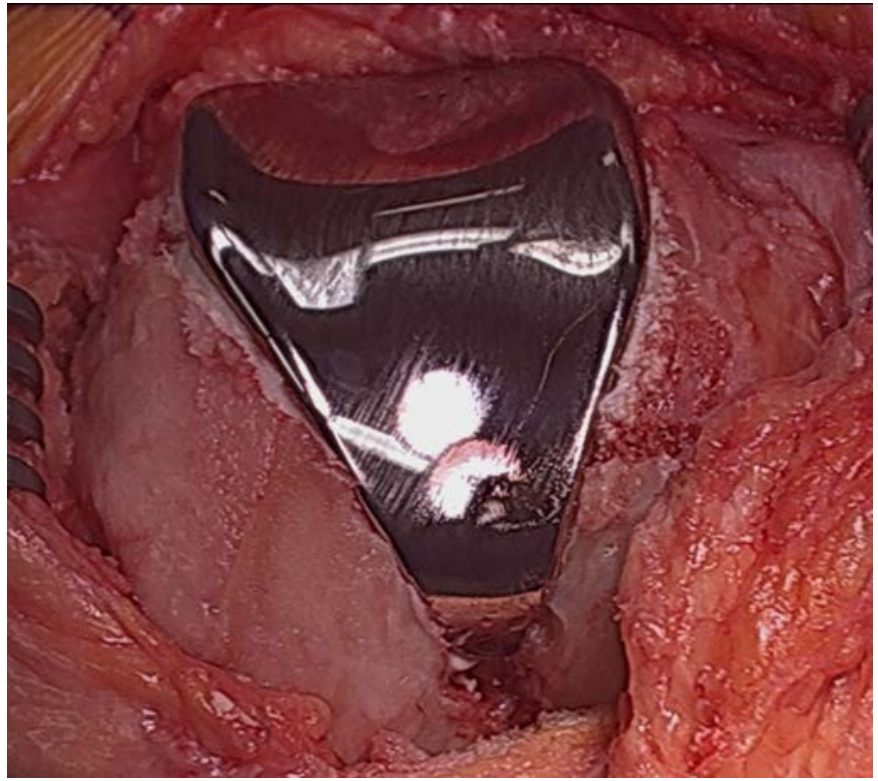
- Match treatment to the pathology – size, depth
- Correct all co-morbidities
- Patient expectations must be reasonable
- Restrain MD ego: we cannot “fix” all patients
- Do not burn bridges

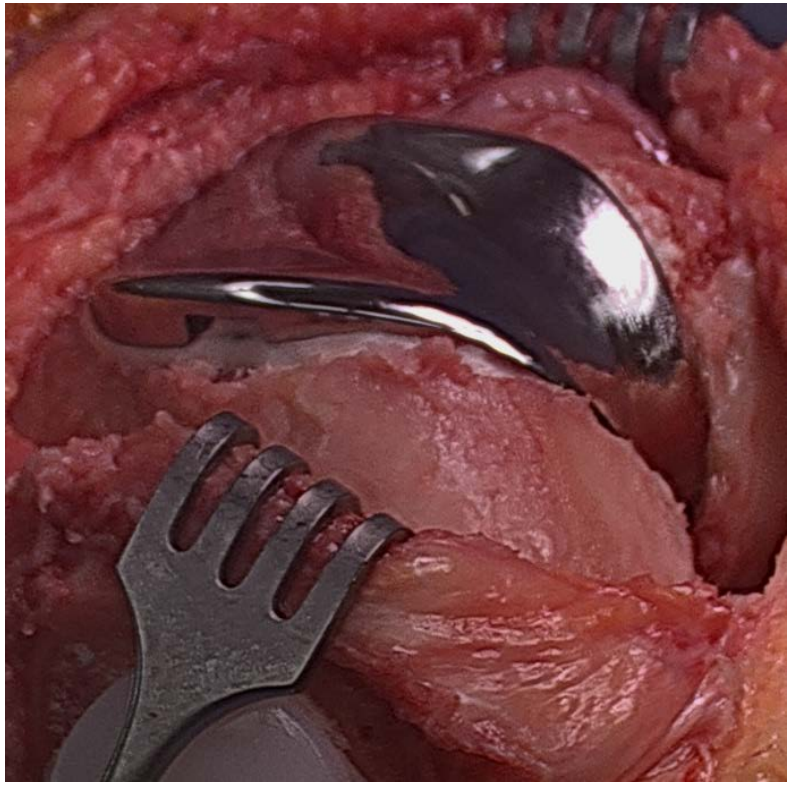
Defect: Instability, Dysplasia, Malalignment





Can’t fix everything with cartilage procedures

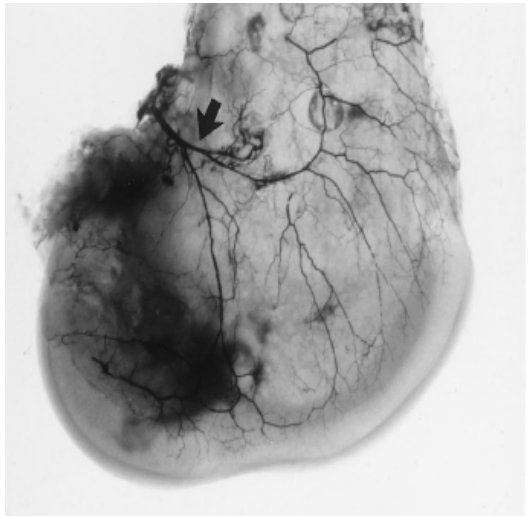


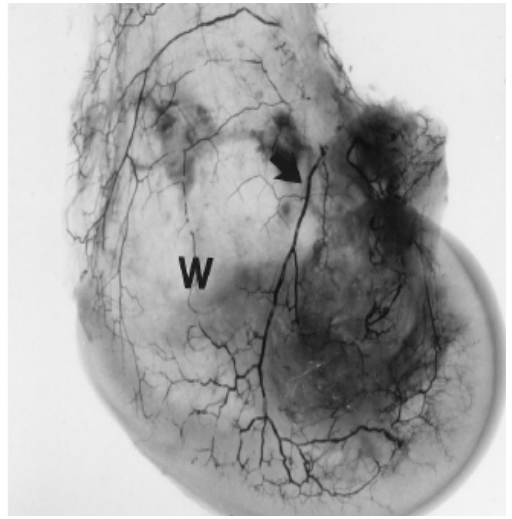


MFC blood supply: single intraosseous artery that leaves “watershed” area

IO pressure in MFC with osteonecrosis (ON) vs without: 62.8 mmHg vs 31.6 mmHg

Average clearance time of contrast with ON vs without:
17.7 min vs 5.5 min

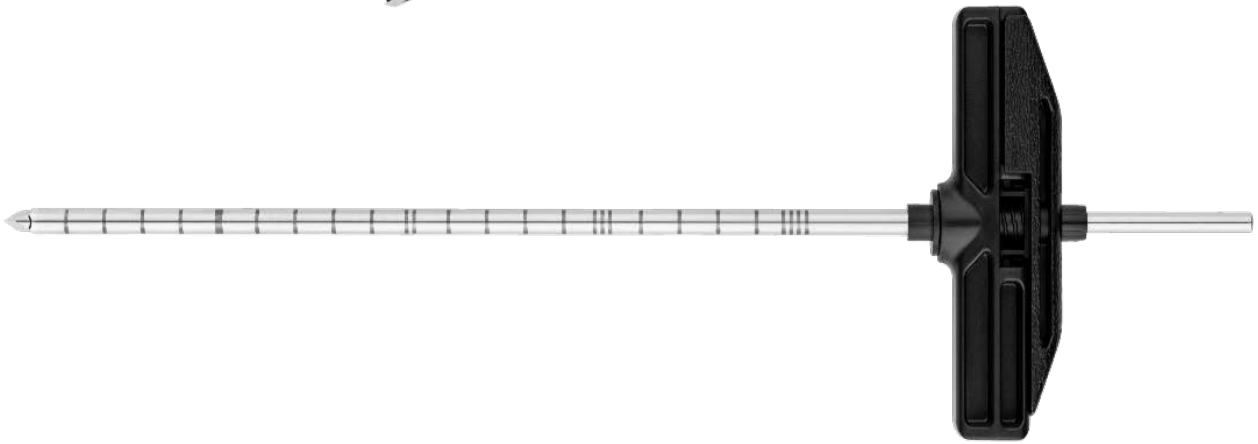




IntraOsseous BioPlasty

Treatment of bone pathologies resulting from acute or chronic injury, including bone marrow lesions and spontaneous osteonecrosis of the knee (SONK). Techniques are intended to encourage physiologic bone remodeling and repair to achieve normal bone and function.

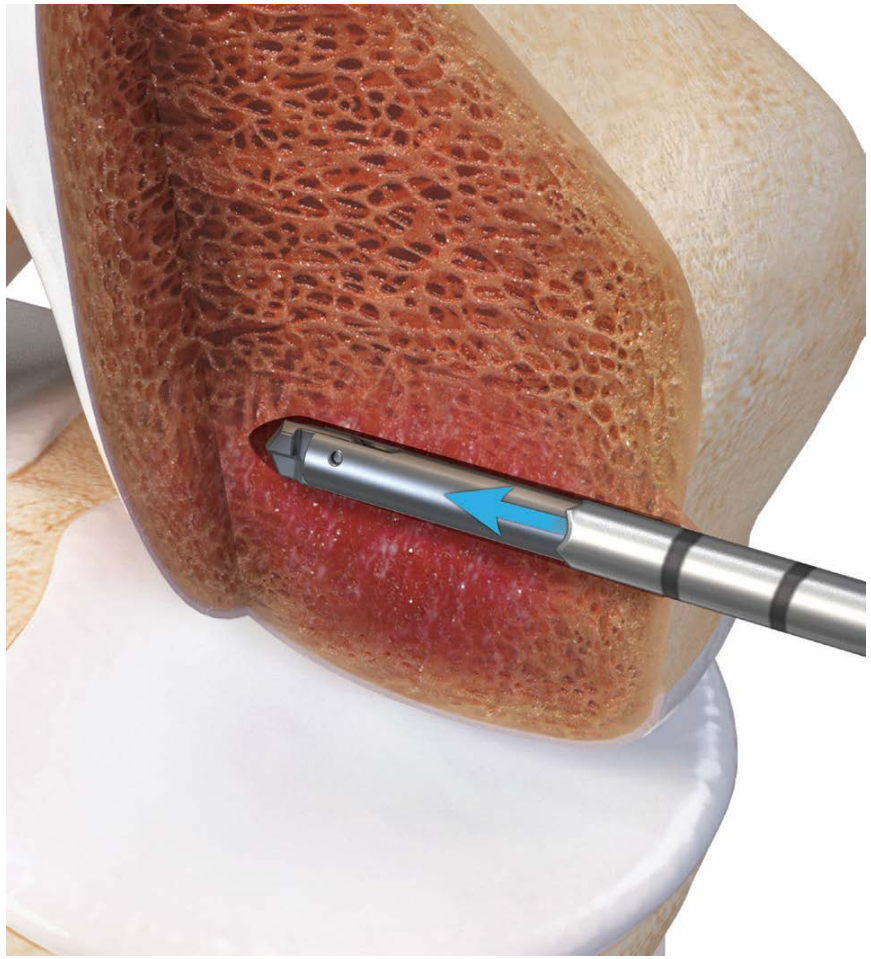
Delivery Cannula Options

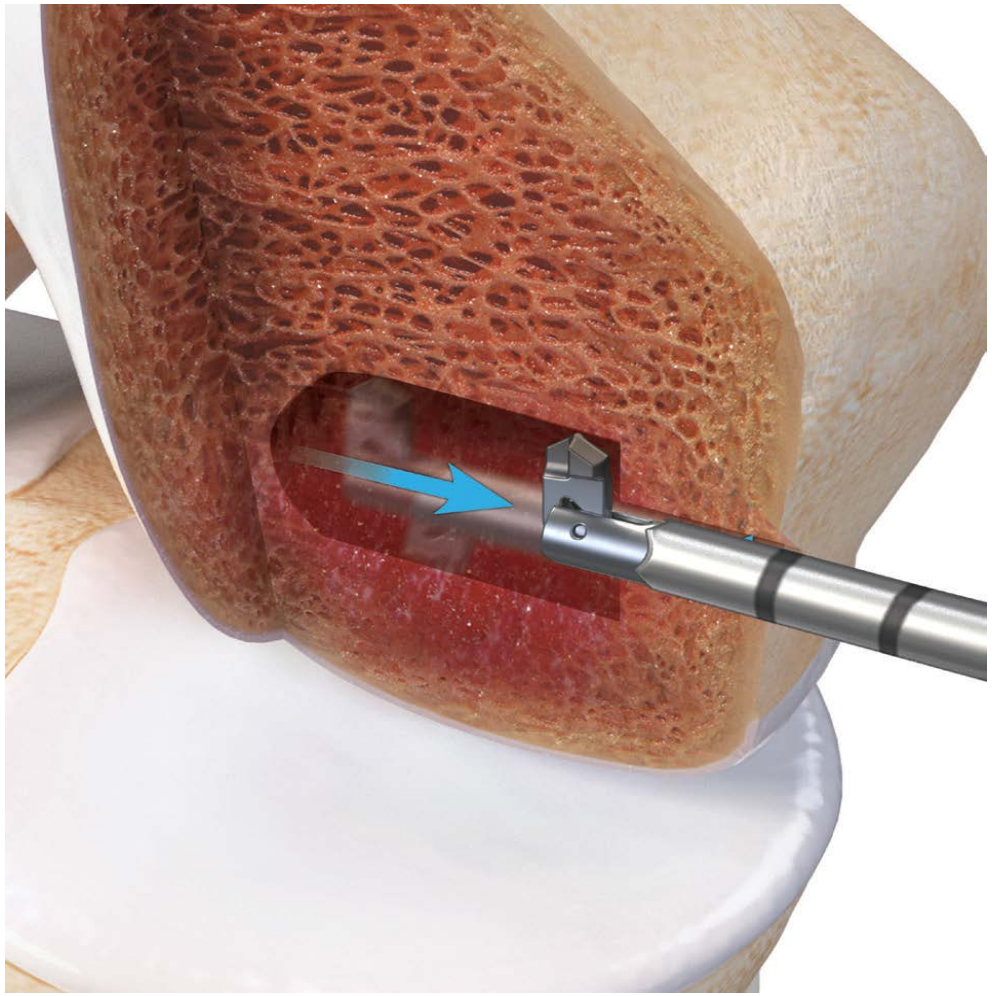


IOBP Decompression Device

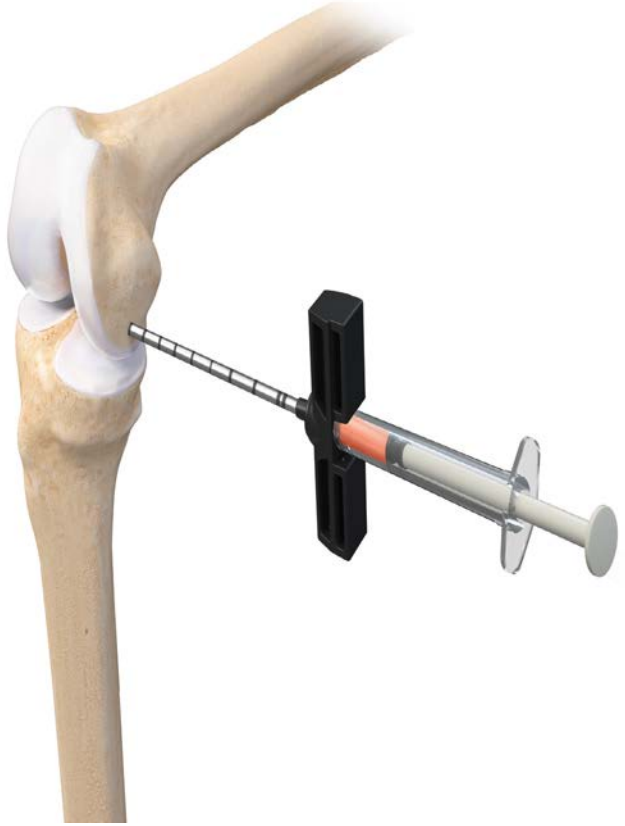
Drilling device

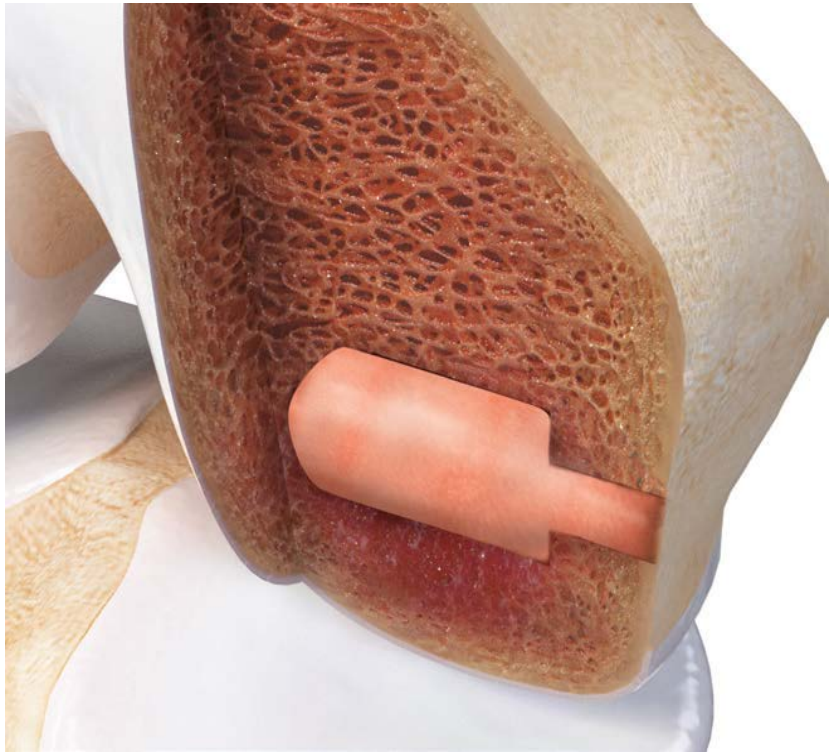
Decompression to 7mm at lesion site





DBM with autologous fluid





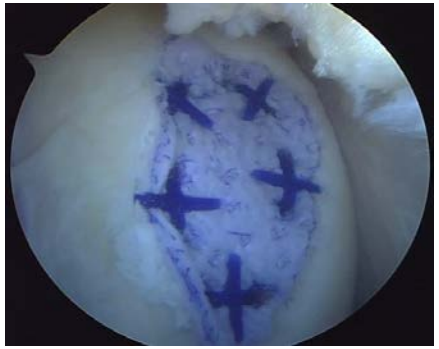
Other treatment methods

DeNovo ET (Zimmer)

- **allogeneic chondrocyte implant**
- **study cancelled in Phase 3 due to enrolment issues**

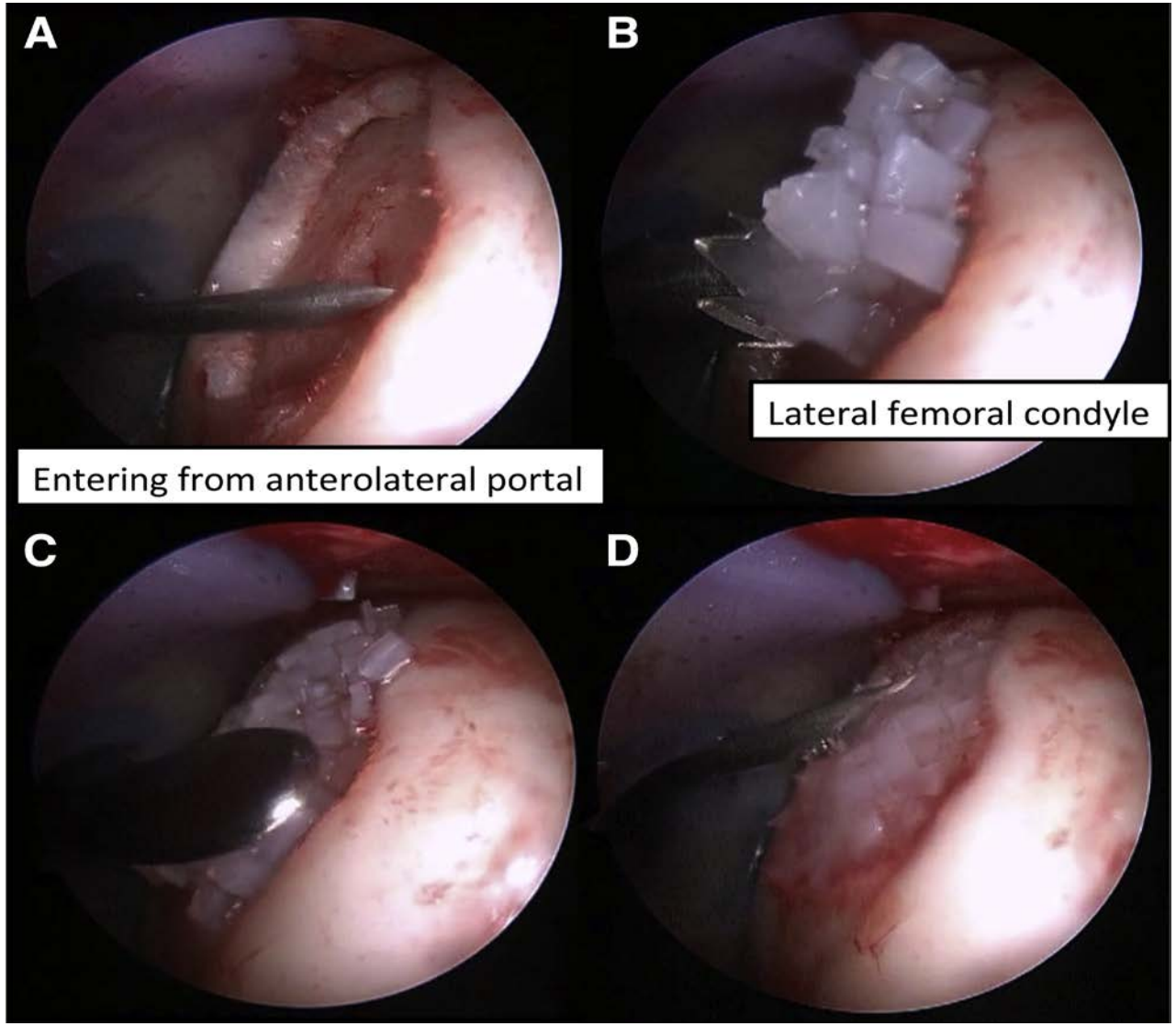
CAIS (DePuy Mitek)

- **particulated cartilage autograft**
- **study cancelled in Phase 3 due to enrolment issues**



Chondrocelect (Tigenix)

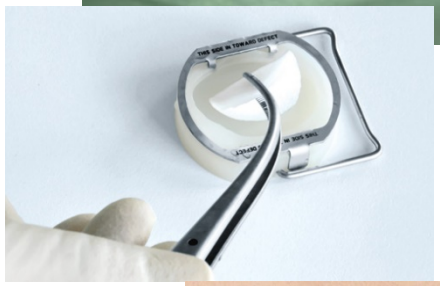
- **ACI variant with optimized culture conditions**
- **Company elected not to start study and close US cell culture facility after discussions with FDA on design**



Arthroscopy Techniques 2019 8e1201-e1207DOI: (10.1016/

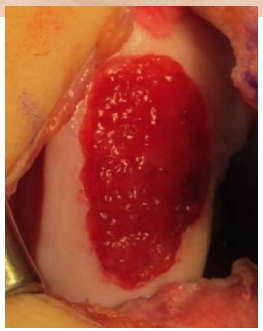
Current Trials

- **Agili-C (Cartiheal)**
  Coral based acellular plug
- **Gelrin C (Regentis)**
  PEG/Fibrinogen hydrogel cured *in situ* with UV



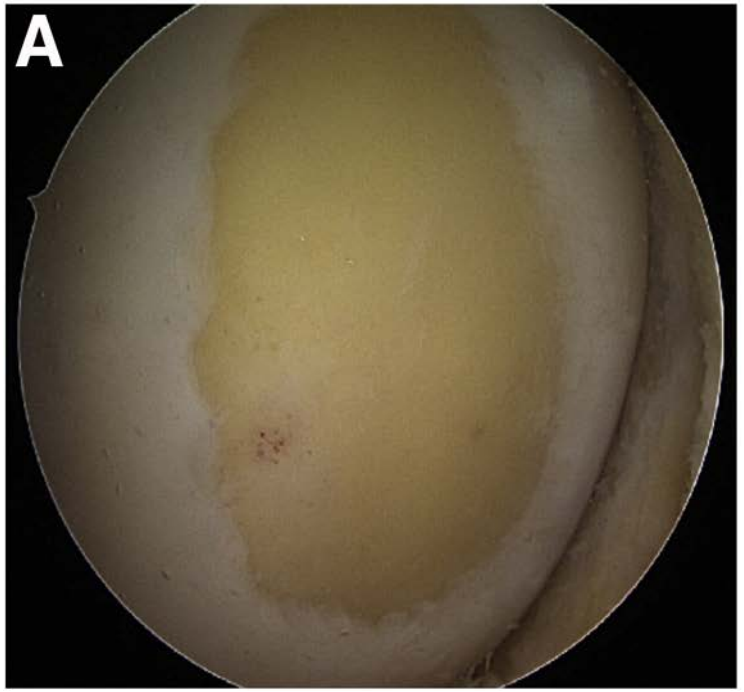
- **Novocart 3D (Aesculap)**
  autologous chondrocyte implant in phase 3
- **Neocart (Histogenics)**
  autologous chondrocyte implant in phase 3

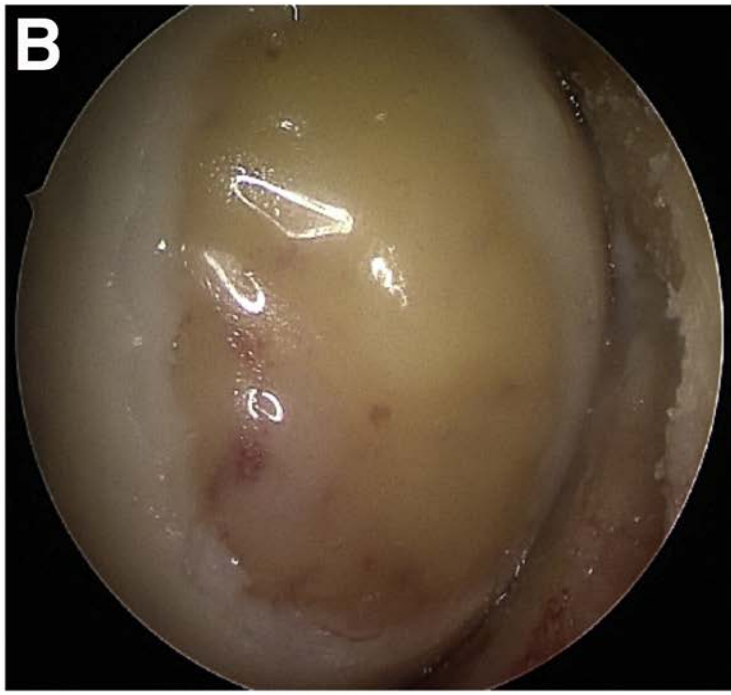
- **Cartistem (Medipost)**
  allogeneic umbilical cord blood stem cells in phase 2
- **Adipose-derived stem cells (Stanford)**
  autologous single-step ADSC RCT against MFx
- **Hyalofast™ (Anika Therapeutics)**
  Nonwoven hyaluronic acid (HA) with BMAC



Agili-C: aragonite based scaffold (calcium carbonate)

Novocart





What to do?

Initial

- Conservative Care
- Drug Treatment
- PT
- Injections

Next

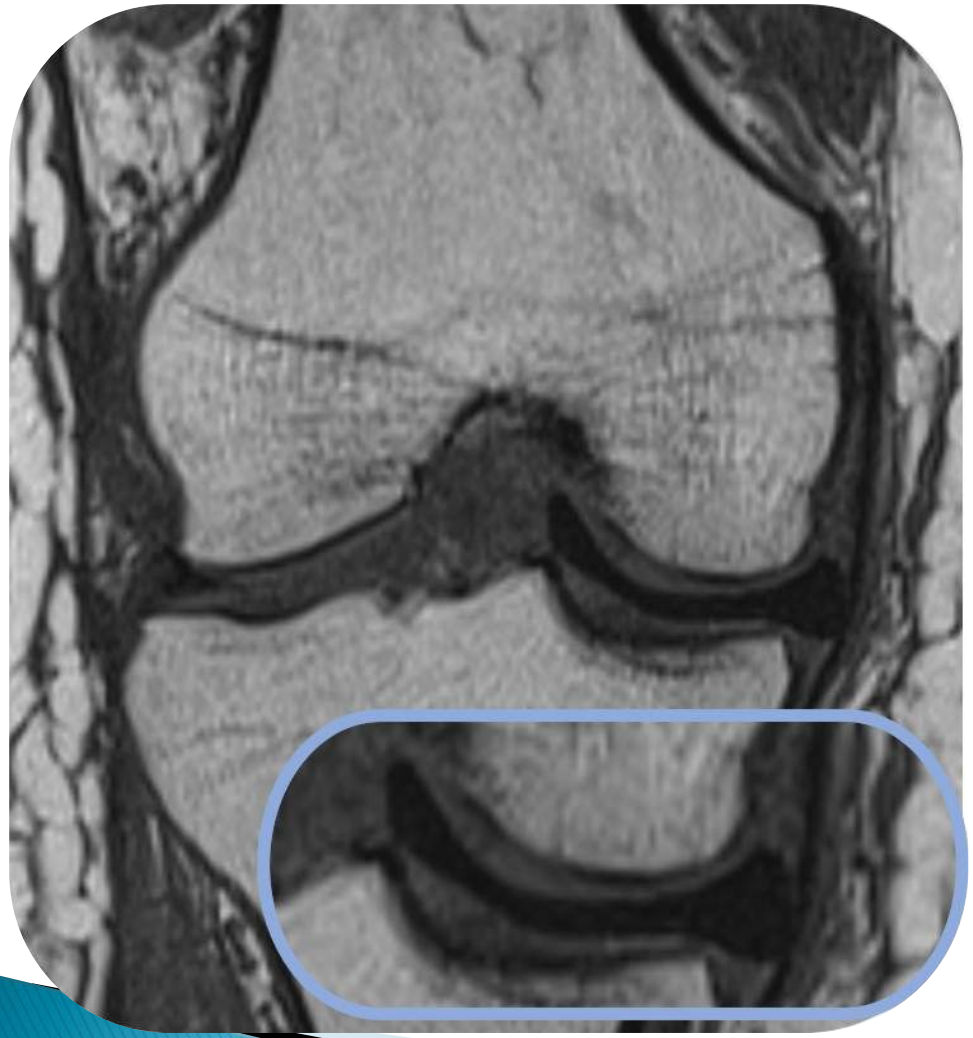
- Repair
- Partial Meniscectomy
- Allograft
- Injections

Fill to Void?

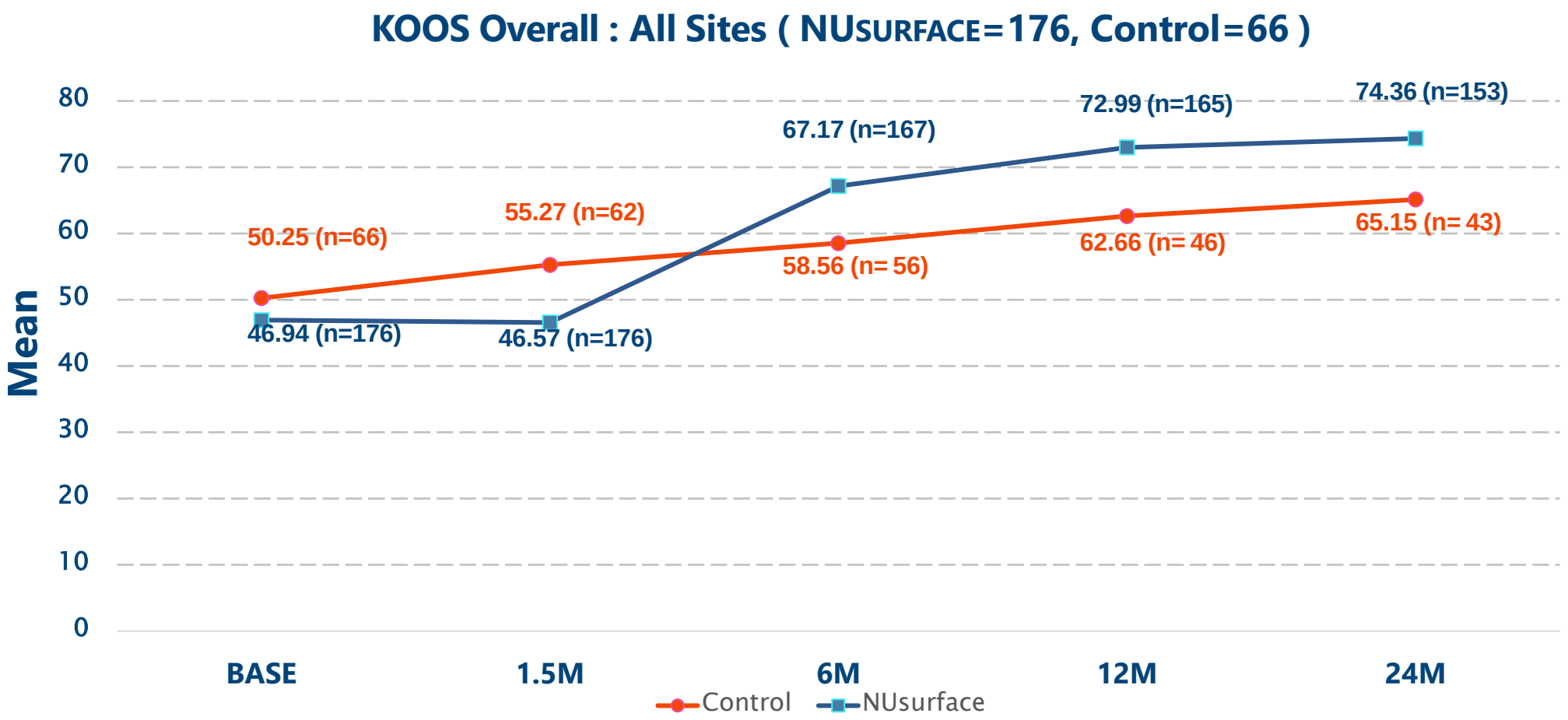
Generally >50 to <70 Years of Age

Final

- **Uni & Total Knee Arthroplasty**



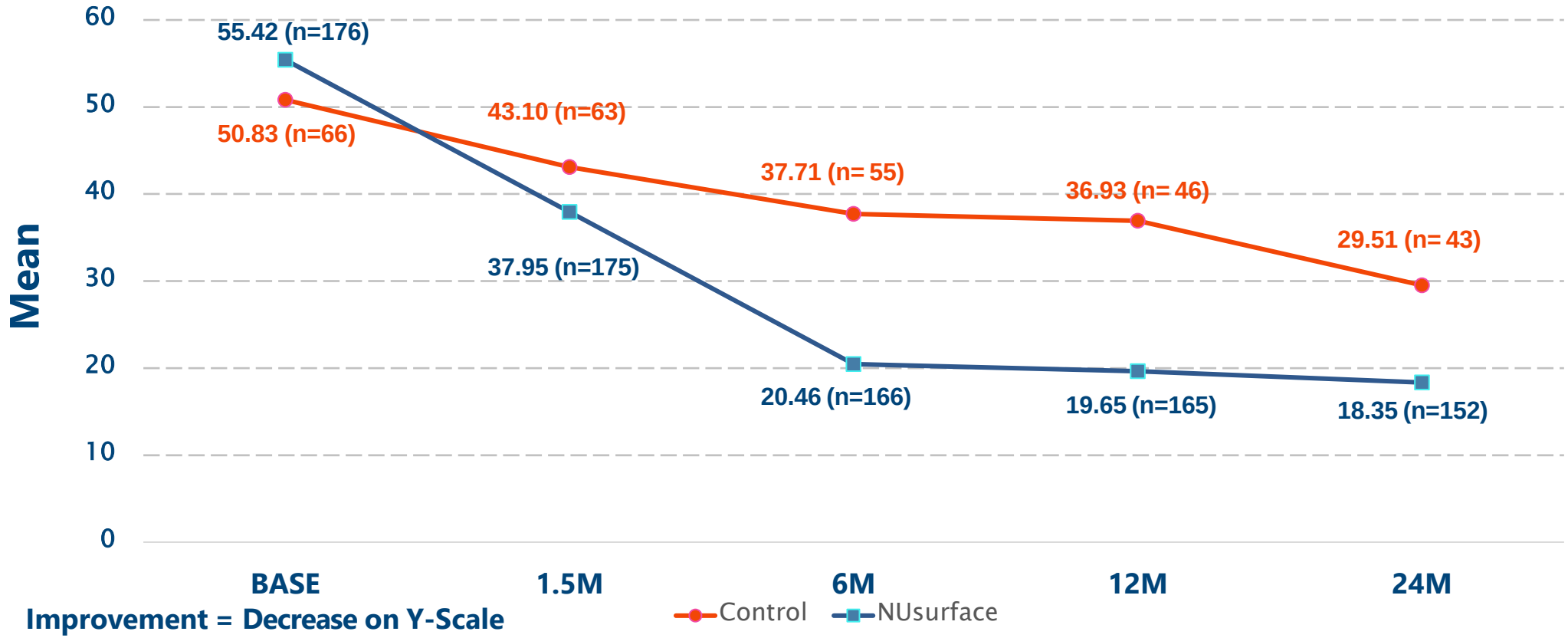
MERCURY | KOOS – Overall



	Baseline	1.5M	6M	12M	24M
CONTROL	50.2566	55.2760	58.5562	62.6571	65.1461
NUSURFACE	46.9424	46.5756	67.1719	72.9945	74.3585

MERCURY | VAS Pain

VAS Pain: All Sites (NUSURFACE =176, Control=66)



Improvement = Decrease on Y-Scale

	Baseline	1.5M	6M	12M	24M
CONTROL	50.8333	43.1048	37.7182	36.9391	29.5140
NUSURFACE	55.4257	37.9494	20.4657	19.6524	18.3501

Adverse Events & Outcomes for NUsurface Subjects with Exchanged Implants

	Primary Implant		Exchanged	
	N	%	N	%
	175		41	
Subsequent Surgical Interventions				
Removals	18	10.3%	4	9.6%
Exchanges	36	20.6%	1	2.4%
Dislocation/Rotation	4	2.3%	0	0
Arthroscopy	8	4.6%	2	4.9%
Symptoms				
Effusion	35	19.9%	3	7.3%
DVT	6	3.4%	0	0
Noise	25		1	2.4%

NUsurface Conclusions

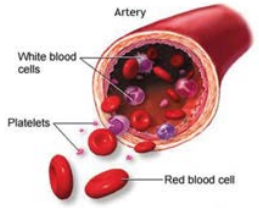
-it does not damage the joint
-subjectively it helps improve symptoms
-encouraging results on the articular cartilage status
-high reoperation rate in early experience

Does the cost/benefit justify its approval and use?

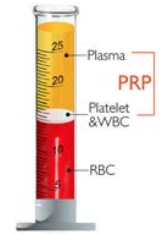
(sounds a lot like meniscal allografts when first started)

Cell Therapy - Orthopaedic Options in the US

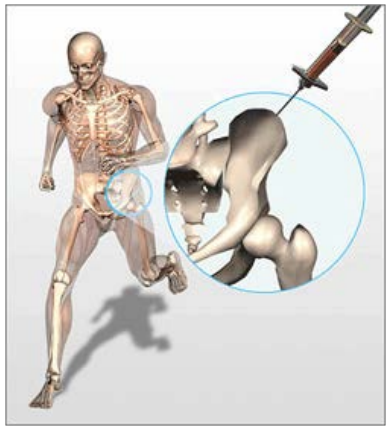
1. Blood



[Blood components]

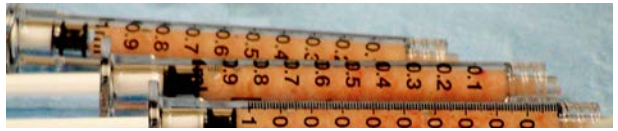


[After centrifugation]



2. Bone Marrow

3. Fat



4. Placenta Products

Thank You