



# What does the Future Hold?

- ① Migrate toward autologous cellular techniques
- ② Migrate away from allograft cellular sources
- ③ Treat subchondral bone lesions
- ④ Use younger chondrocytes



# 1 Migrate toward: Cellular Therapy

- Chondrocytes

- ✓ DeNovo
- ✓ Cartiform
- ✓ MACI
- ✓ Osteochondral Autograft
- ✓ Osteochondral Allograft

- Progenitor cells

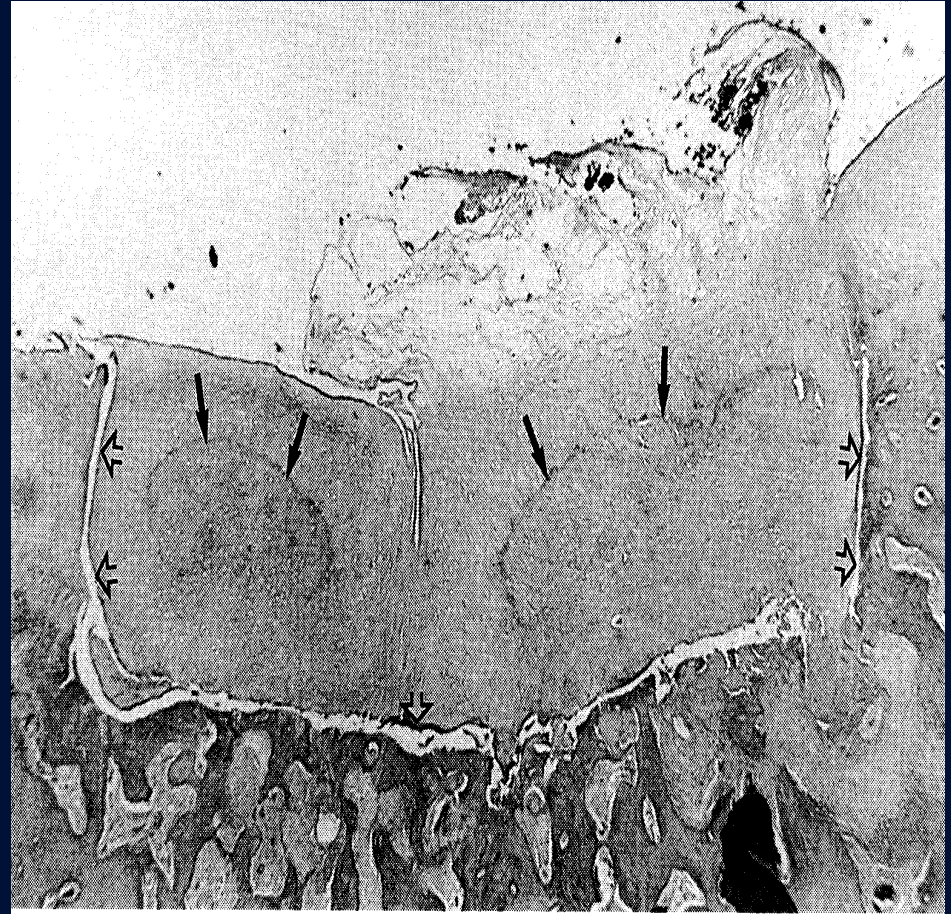
- ✓ ~~Microfracture~~ Bone Marrow Derived Cells (BMAC)
- ✓ ~~Microdrilling~~ Adipose Derived Cells (ADSC)





# Why use stem cells?

- Adult differentiated cells retain zonal memory
- Require isolation and seeding by zone
- Difficult to adhere to native tissue





# Where are Stem Cells found in Bone Marrow?

- In Bone Marrow, MSCs are found near medullary venous sinuses
- Can mobilize into circulation
- Must disrupt local environment to dislodge cells

40  $\mu\text{m}$



# Bone Marrow Aspiration Technique

- Quickly retract syringe plunger
- High negative pressure=more MSCs
- MSC number ↓ with higher volume
- Keep low aspiration volume (1-4mL)

## Muschler Data:

1mL aspirate= 1451 CFU/mL

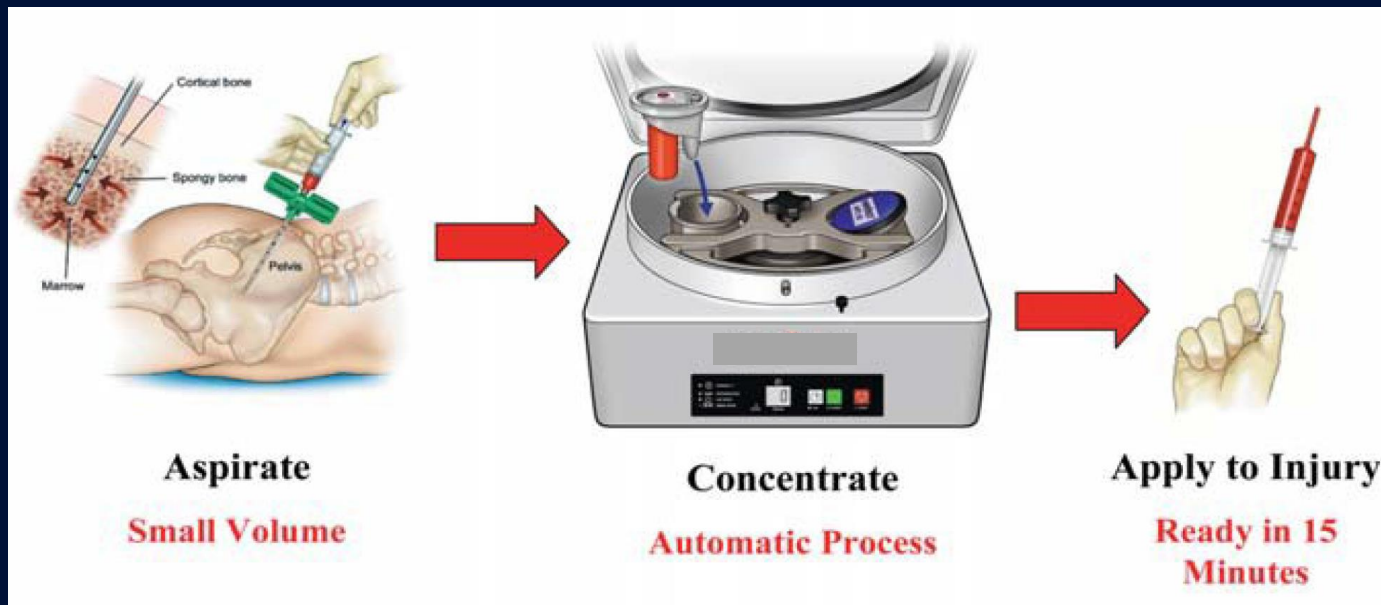
2mL aspirate= 1051-1418

4mL aspirate= 882



# Bone Marrow Aspiration Concentration

- Bone marrow aspirate contains few progenitor cells **0.01% or 1 in 100,000 cells**
- Centrifuge can be used to increase MSCs





# One-Step Surgery With Multipotent Stem Cells for the Treatment of Large Full-Thickness Chondral Defects of the Knee

Alberto Gobbi,<sup>\*†</sup> MD, Georgios Karnatzikos,<sup>†</sup> MD, and Sukesh Rao Sankineani,<sup>†</sup> MD  
*Investigation performed at the Orthopaedic Arthroscopic Surgery International (OASI) Bioresearch Foundation, Milan, Italy*

- BMAC + ChondroGide patch + suture
- Mini-arthrotomy
- Results:
  - KOOS pain: 61 to **93**
  - KOOS ADL: 64 to **91**
  - VAS: 5.4 to **0.5**







# Where are Stem Cells found in Adipose Tissue?

- Perivascular cells: **Pericytes**
- High concentration in fat
- **Stromal vascular fraction (SVF)**

- Harvest of MSCs (pericytes) requires disruption of local vascular tissue

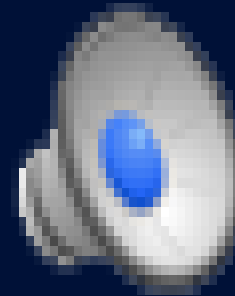
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# Abdominal Harvest

- Tumescant Liposuction
- Can be performed in clinic
- Allow plenty of time between injection and harvest

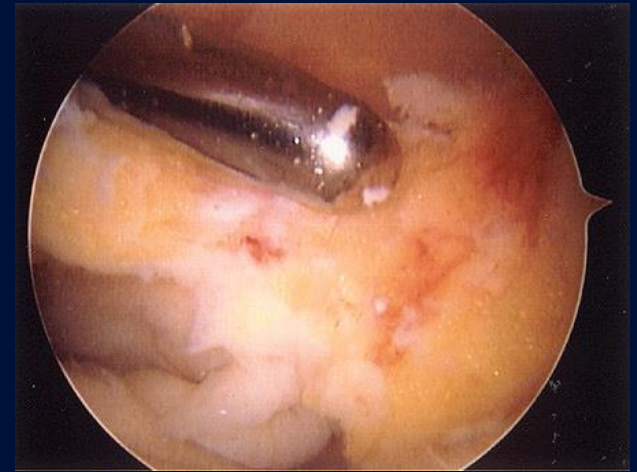




# Fat Pad Harvest

## Arthroscopic Harvest of Adipose-Derived Mesenchymal Stem Cells From the Infrapatellar Fat Pad

Jason L. Dragoo,\*† MD, and Wenteh Chang,† PhD  
*Investigation performed at the Department of Orthopaedic Surgery,  
Stanford University School of Medicine, Stanford, California, USA*



## Tissue-engineered cartilage and bone using stem cells from human infrapatellar fat pads

J. L. Dragoo, B. Samimi, M. Zhu, S. L. Hame, B. J. Thomas, J. R. Lieberman,  
M. H. Hedrick, P. Benhaim

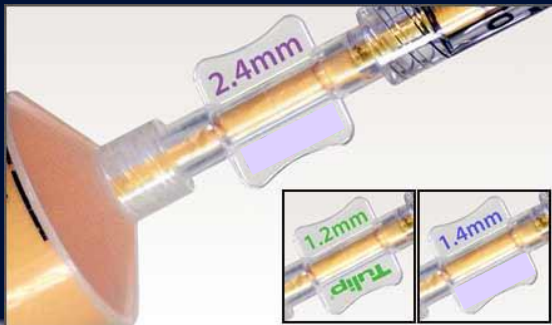
*From the UCLA Medical Centre, Los Angeles, USA*



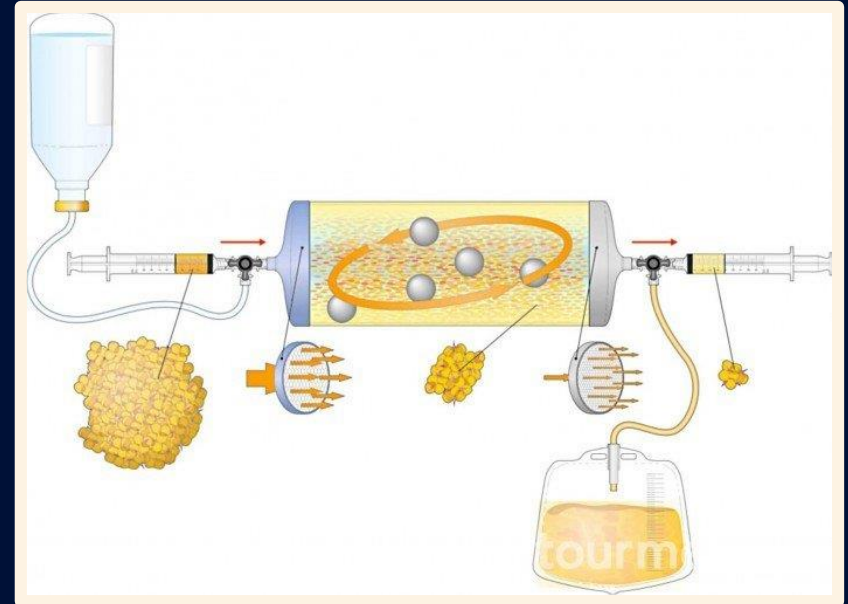


- Fractionation of adipose tissue required
- Releases MSCs from their vessels/matrix

## Syringe Emulsification



## Ball Bearing System

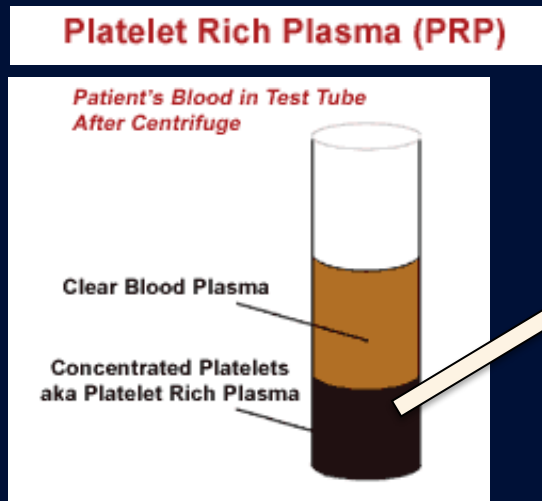






# Potential Synergy with PRP?

- PDGF-BB found in PRP releases pericytes from attachment on vessel wall



pdgf-b<sup>ret/ret</sup>

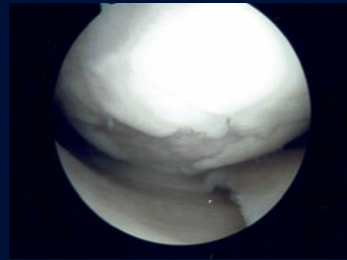


Pericytes= Black

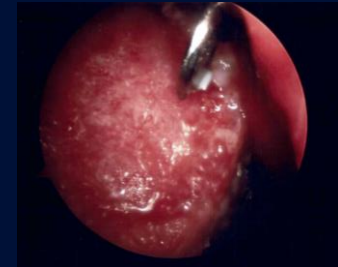


# Arthroscopic Stem Cell Technique

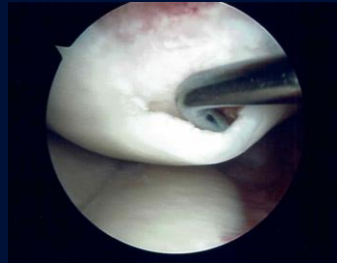
Initial lesion



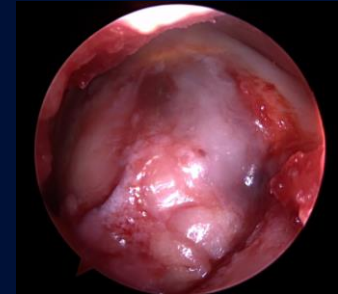
Add base layer of fibrin glue



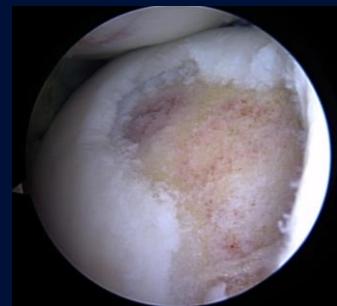
Fibrin glue may help seal delaminating cartilage



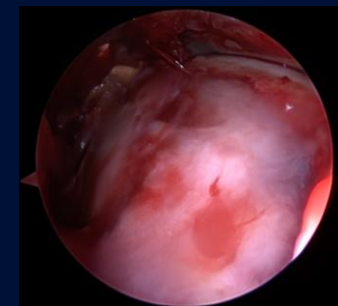
Add Matrix, then ADSCs with Craig biopsy needle



Remove calcified cartilage layer and then saline

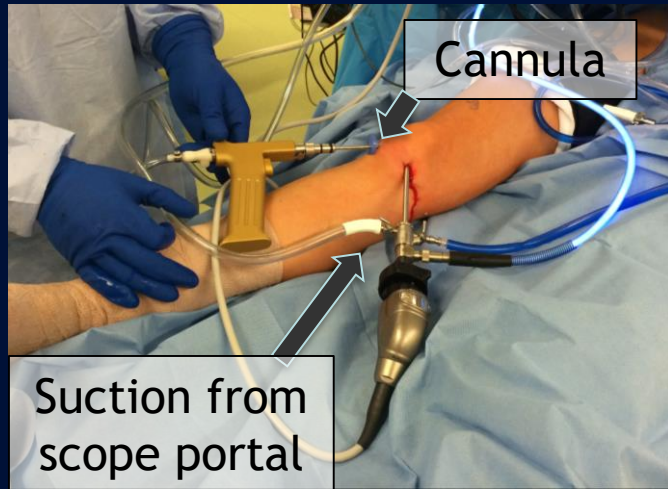


Seal with additional layer of fibrin glue





# Arthroscopic Cartilage Technique



Arthroscopic set up



Flexible cannula to retract soft tissue





# Human RCT: Chondral Defect

## Stem Cell Treatment

- Arthroscopically harvested ADSCs
- Cell concentration
- Autologous fibrin glue
- **FDA** approved matrix
- **No marrow stimulation**

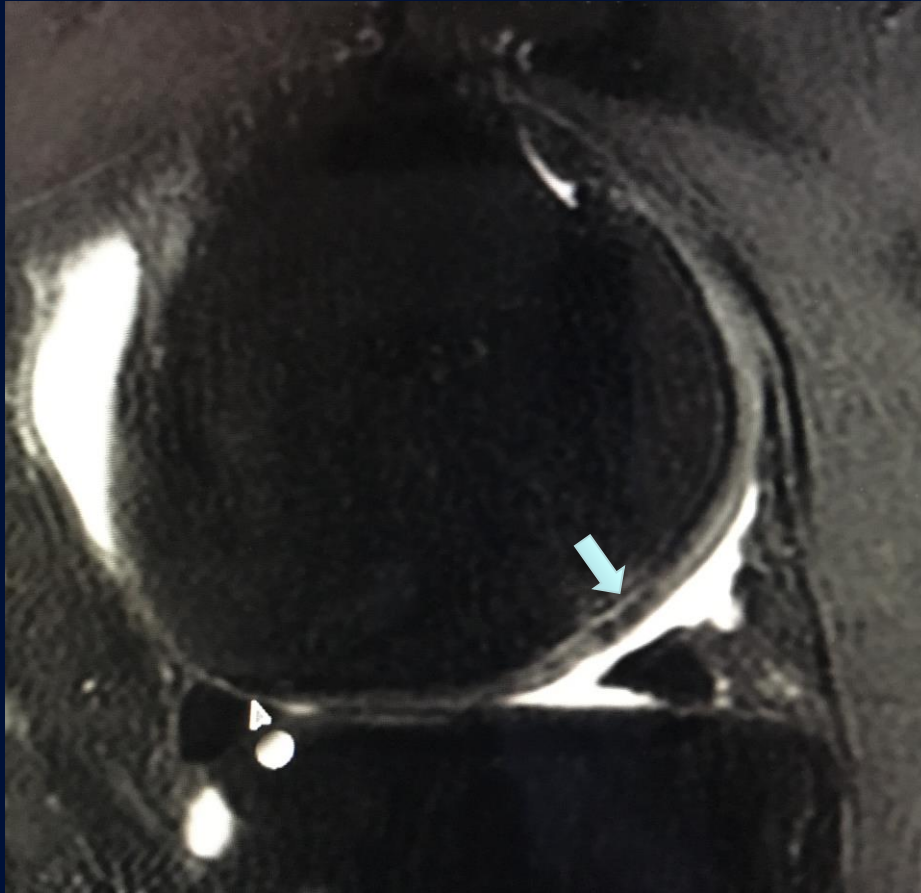
## Microdrilling plus

- Std treatment
- **FDA** approved matrix
- 8 weeks TDWB
- Stratified for lesion size

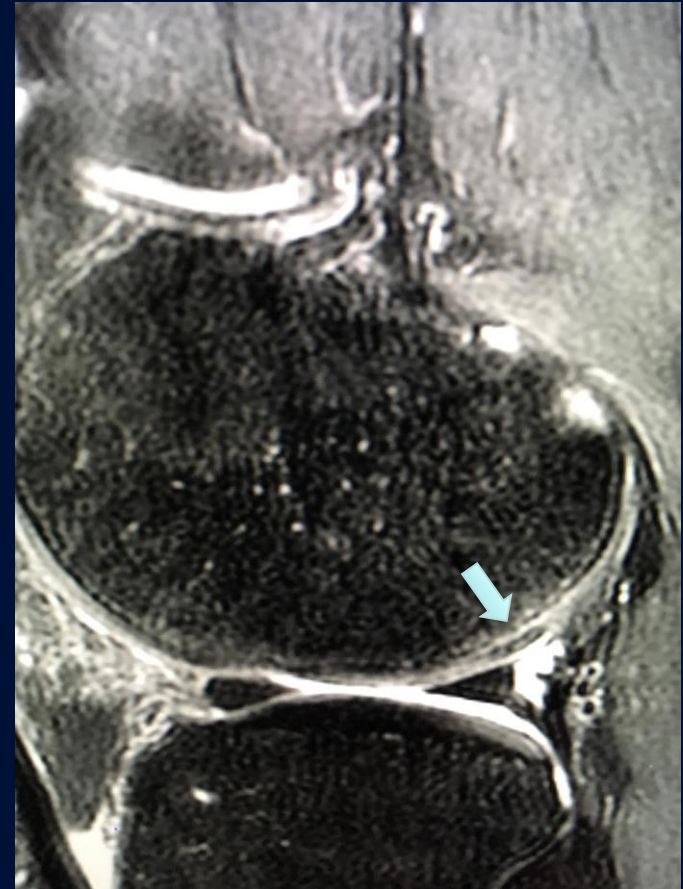
**Outcome measures:** KOOS, VAS, MRIs- T1 $\rho$  and T2 Map  
@ 6mo, 1, 2 yr follow-up



# Cartilage Defect Study



Patient 1



Patient 2





# Intra-articular Injection of Mesenchymal Stem Cells for the Treatment of Osteoarthritis of the Knee

## A 2-Year Follow-up Study

Chris Hyunchul Jo,\* MD, Jee Won Chai,† MD, Eui Cheol Jeong,‡ MD, Sohee Oh,§ PhD, Ji Sun Shin,\* BS, Hackjoon Shim,|| PhD, and Kang Sup Yoon,\*\* MD  
Investigation performed at the Seoul Metropolitan Government–Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Republic of Korea

- $1 \times 10^8$  ADSCs
  - ✓ Open harvest
  - ✓ Cultured 3 weeks
- n=18 patients
- Results:
  - ✓ WOMAC: 49.9 → 30.3
  - ✓ Lysholm: 40.1 → 73.4

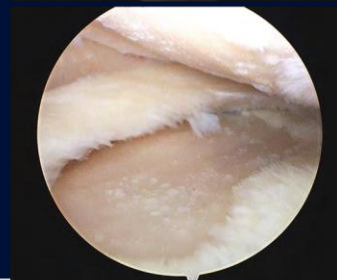
### ADSC Injection

Pre injection

Post injection @ 6mo

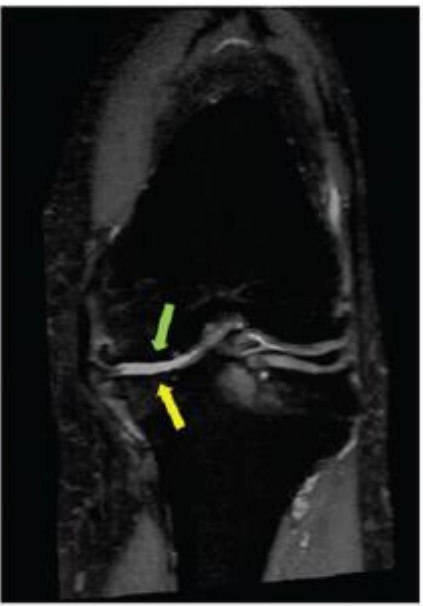
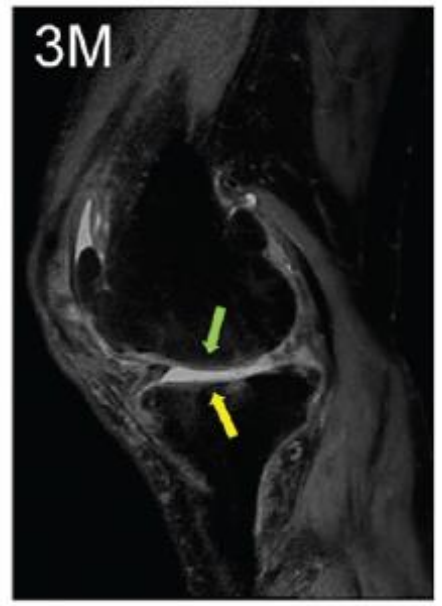
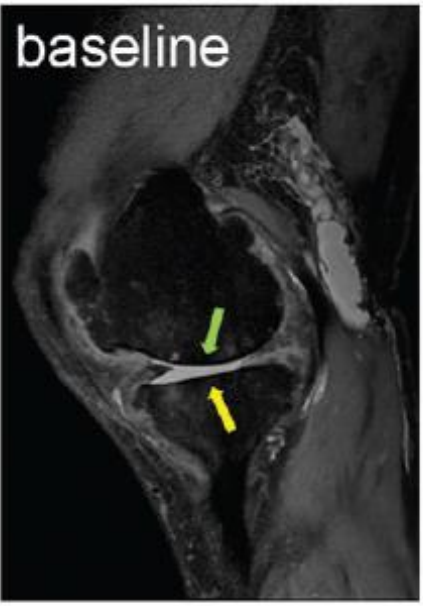


Femur  
Medial



Tibia







# Human RCT: OA

## Stem Cells + Arthroscopy

- Arthroscopically harvested ADSCs
- Cell concentration
- Removal of calcified cartilage
- Gentle chondroplasty
- Injection after closure

## Arthroscopy alone

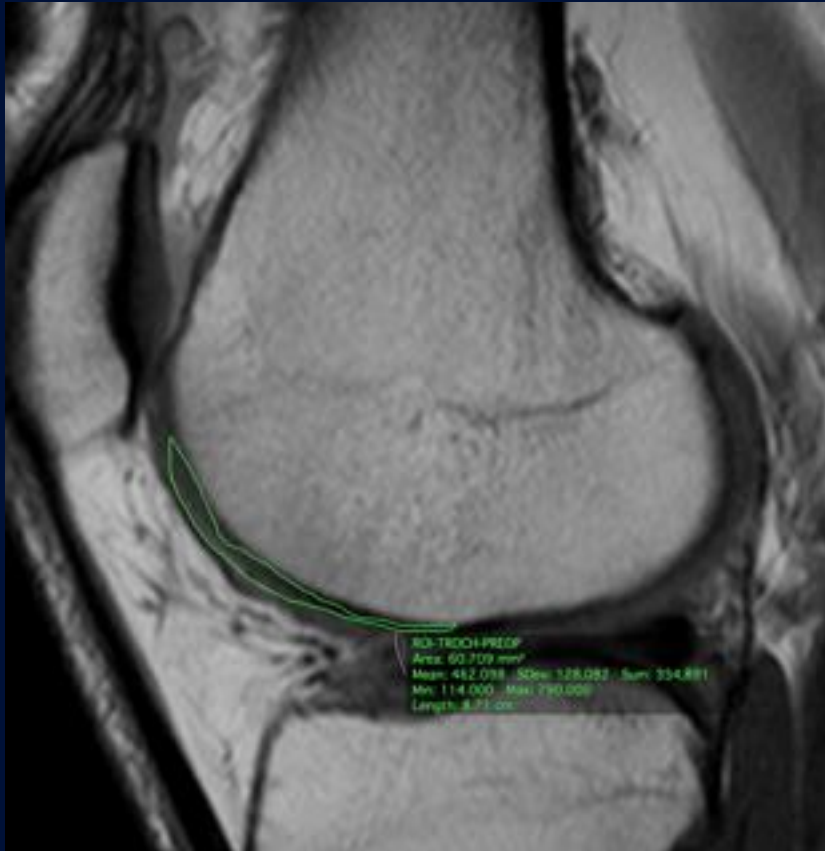
- Std treatment: meniscectomy, synovectomy, LB
- 4 days TDWB/full ROM
- Saline injection

**Outcome measures:** KOOS, VAS, MRIs- T1 $\rho$  and T2 Map @ 6mo, 1, 2 yr follow-up





# OA Trial Early Results





# Amniotic Fluid and Cells

## Amniotic Mesenchymal Stromal Cells Exhibit Preferential Osteogenic and Chondrogenic Differentiation and Enhanced Matrix Production Compared With Adipose Mesenchymal Stromal Cells

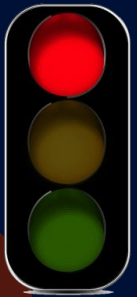
Natasha Topoluk,\* PhD, Richard Hawkins,\*† MD, John Tokish,\*† MD, and Jeremy Mercuri,\*\*† PhD  
*Investigation performed at Laboratory of Orthopaedic Tissue Regeneration & Orthobiologics, Department of Bioengineering, Clemson University, Clemson, South Carolina, USA*

- Data suggests that harvest from the delivery room:
  - ✓ Large number of Multipotent cells
  - ✓ Good GF content





# Amniotic Fluid and Cells



The majority of placental tissue allografts available **contain no living cells** as a result of processing, preservation, and sterilization methods. The observed beneficial effects of such products are not mediated by MSCs but might be linked to the **placental ECM and/or growth factors and cytokines** present in the tissue.

2017 McIntyre

- Use cannot be recommended



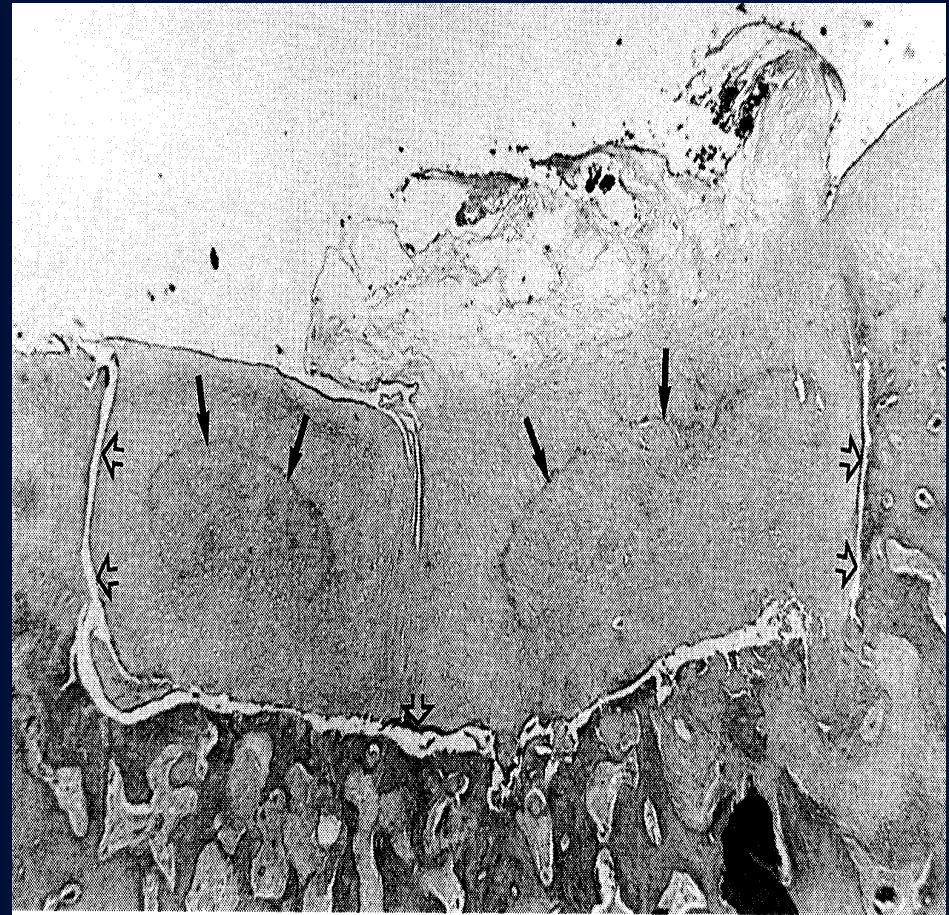
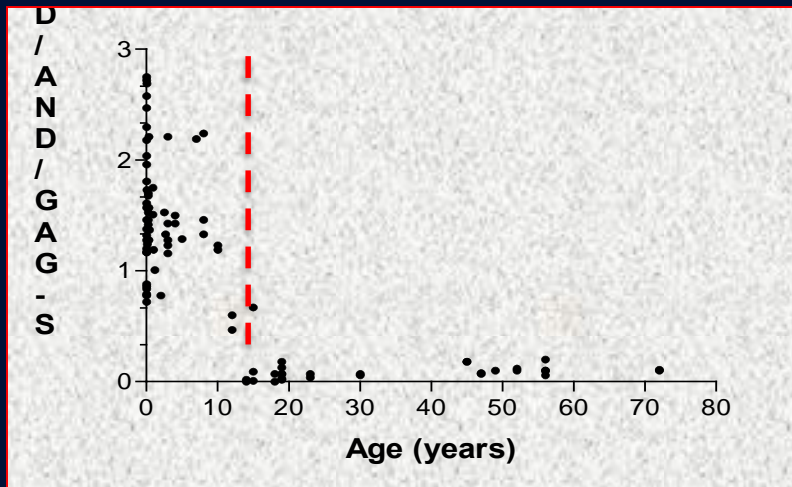
# 3 Treat Subchondral Bone lesions





# 4 If you use chondrocytes, use younger ones

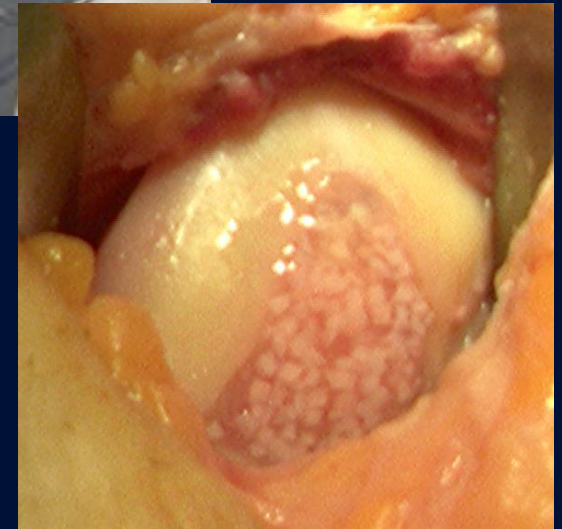
- Metabolic activity of chondrocytes decreases at age 13





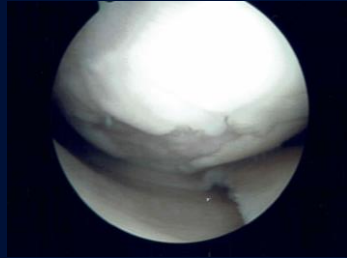
# Juvenile Chondrocytes

- Minced **allogeneic** chondrocytes
  - ✓ Age less than age 13
  - ✓ Secured with fibrin glue
  - ✓ Can be performed arthroscopically

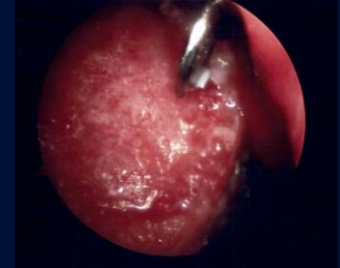


# Arthroscopic JC Technique

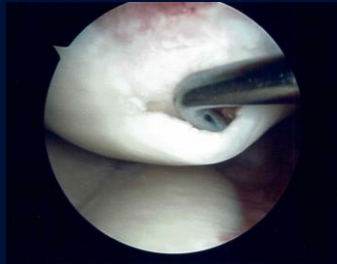
Initial lesion



Add base layer of fibrin glue



Fibrin glue may help seal delaminating cartilage



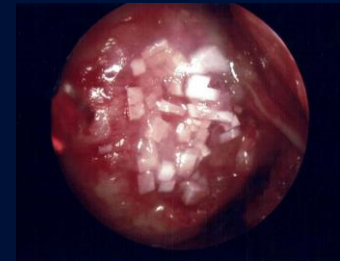
Add DeNovo with freer or Craig biopsy needle



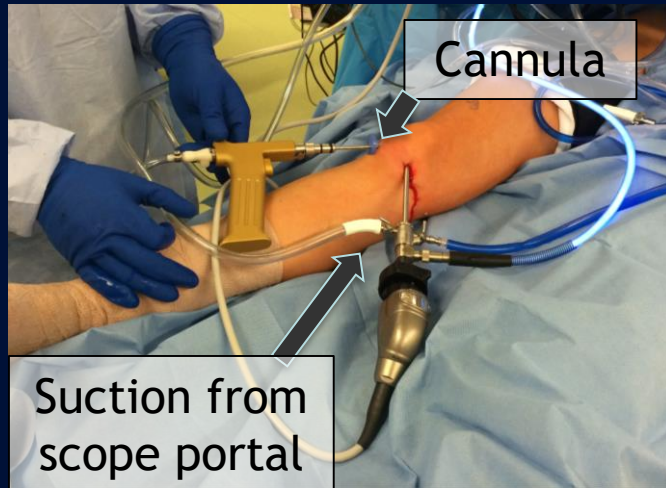
Remove calcified cartilage layer and then saline



Seal with additional layer of fibrin glue



# Arthroscopic Technique



Arthroscopic set up



Flexible cannula to retract soft tissue





# Evidence

- Farr, J (AJSM 2014)
  - **Level IV**, 25 patients
  - Clinically improved at 2 yrs
  - 1 graft delamination
- Buckwalter, J (Iowa Ortho J 2014)
  - **Level IV**, 17 patients patellar lesions
  - Clinically improved at 8 mo



# Current Environment

- >570 (1,000's) stem cell clinics are operating
  - Most are PM&R
  - Anesthesiologists
  - Family Practice
- Promising therapy is drowned out by CASH clinics
- Affecting patient opinions and FDA regulation



# FDA Enforcement

"I've directed the FDA to launch a new working group to pursue unscrupulous clinics through whatever legally enforceable means are necessary to protect the public health," Gottlieb wrote. "We have examples where some of these unproven treatments have clearly harmed patients." This year, [a paper](#) published in the New England Journal of Medicine recounted how three women, ages 72 to 88, with macular degeneration were left blind after a stem cell treatment at an unnamed clinic in Florida in 2015.

"There are important distinctions to be made, and the FDA seems to be making these distinctions in terms of suggesting that they are putting together this working group, a task force, going after businesses marketing unproven interventions, going after businesses making illegitimate or unwarranted claims about stem cell treatment," he said.





# FDA Enforcement

## FDA News Release

### **FDA seeks permanent injunctions against two stem cell clinics**

*Actions part of a comprehensive approach to the oversight of regenerative medicine products*

## **For Immediate Release**

May 9, 2018

## **Release**

The U.S. Food and Drug Administration, in two complaints filed today in federal court, is seeking permanent injunctions to stop two stem cell clinics from marketing stem cell products without FDA approval and for significant deviations from current good manufacturing practice requirements.

“Cell-based regenerative medicine holds significant medical opportunity, but we’ve also seen some bad actors leverage the scientific promise of this field to peddle unapproved treatments that put patients’ health at risk. In some instances, patients have suffered serious and permanent harm after receiving these unapproved products. In the two cases filed today, the clinics and their



# FDA Enforcement Priorities

## Tiered risk-based approach to enforcement:

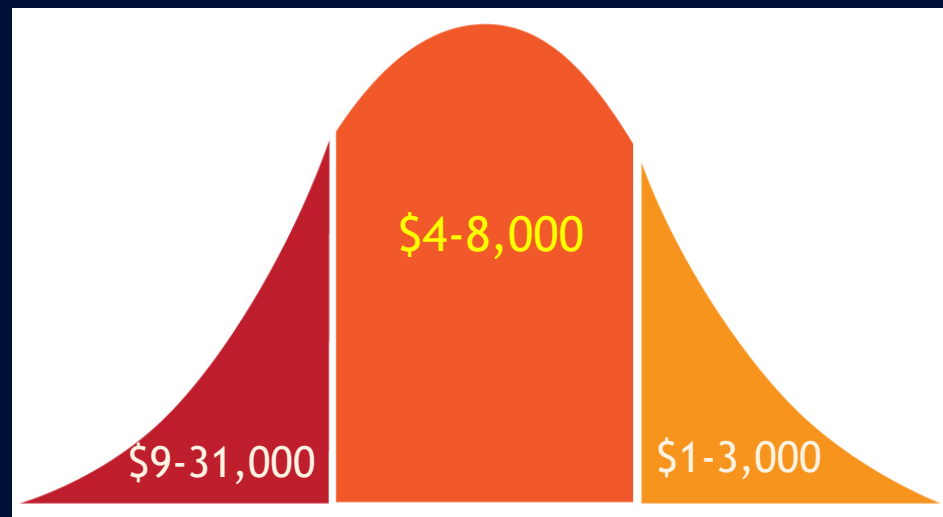
1. Transmission of communicable disease
2. Preventing contamination during processing
3. Assuring product safety, integrity, function and efficacy maintained after processing
4. Higher risk routes of administration: Intra-thecal, IV

Musculoskeletal administration into joints and “orthopedic tissues” not on the top 10 list



# What do Biologics treatments cost?

- Cash Only
- No CPT codes except:
  - ✓ Limited musculoskeletal US (76882)
  - ✓ US guided injection (76942)





# Billing Principles

- The use of biologics is generally considered investigational and of unproven benefit and thus, 3<sup>rd</sup> party payers will not routinely reimburse for the procedure (CPT code) or the substance being injected
- Medicare **considers these non-covered services** and the **ABN** is.... considered best practice

Courtesy of Brian Cole, MD





# Advanced Beneficiary Notice (ABN)

**G. OPTIONS:** Check only one box. We cannot choose a box for you.

- OPTION 1.** I want the D. \_\_\_\_\_ listed above. You may ask to be paid now, but I also want Medicare billed for an official decision on payment, which is sent to me on a Medicare Summary Notice (MSN). I understand that if Medicare doesn't pay, I am responsible for payment, but I can appeal to Medicare by following the directions on the MSN. If Medicare does pay, you will refund any payments I made to you, less co-pays or deductibles.
- OPTION 2.** I want the D. \_\_\_\_\_ listed above but do not bill Medicare. You may ask to be paid now as I am responsible for payment. I cannot appeal if Medicare is not billed.
- OPTION 3.** I don't want the D. \_\_\_\_\_ listed above. I understand with this choice I am not responsible for payment, and I cannot appeal to see if Medicare would pay.

**H. Additional Information:**

**This notice gives our opinion, not an official Medicare decision.** If you have other questions on this notice or Medicare billing, call **1-800-MEDICARE** (1-800-633-4227/TTY: 1-877-486-2048).

Signing below means that you have received and understand this notice. You also receive a copy.

**I. Signature:**

**J. Date:**

According to the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number. The valid OMB control number for this information collection is 0938-0566. The time required to complete this information collection is estimated to average 7 minutes per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. If you have comments concerning the accuracy of the time estimate or suggestions for improving this form, please write to: CMS, 7500 Security Boulevard, Attn: PRA Reports Clearance Officer, Baltimore, Maryland 21244-1850.



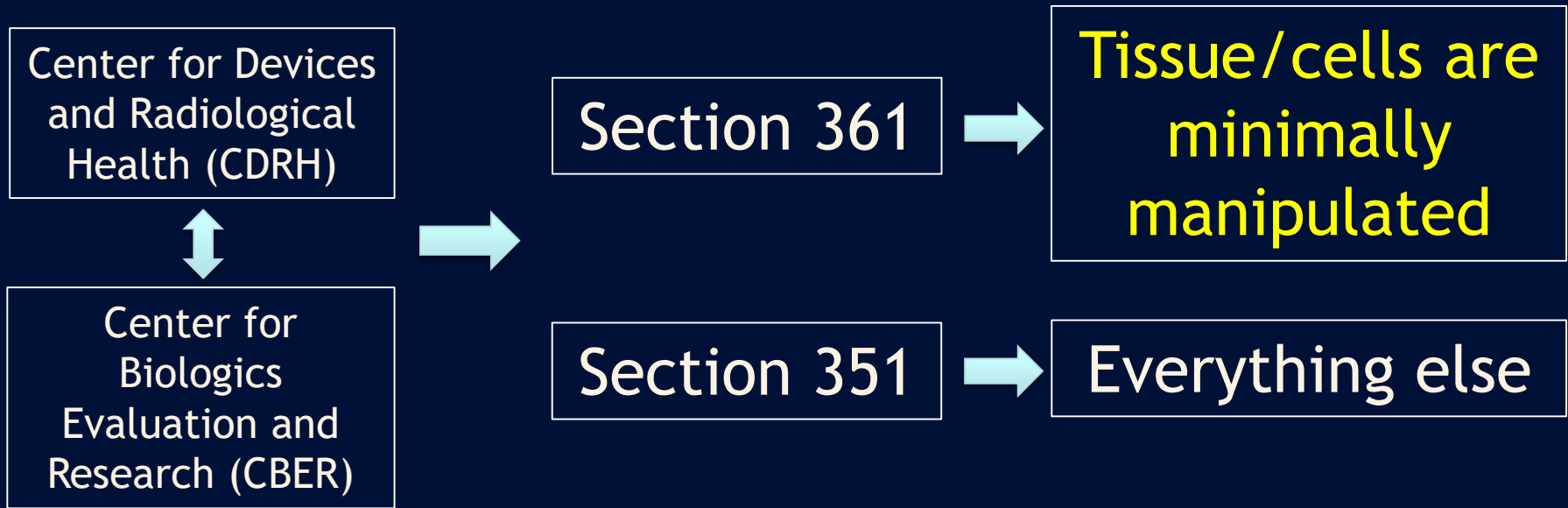


# Office Billing or Isolated Surgical Procedure *For BMAC, Adipose, Amniotic*

- If **non-coverage**, offer copy of policy to patient supporting notion that it can be **self-pay**.
- **Sign ABN** to allow direct billing if physician takes Medicare (or other government payer) assignment.
- Can bill patient for **procedure, substance, injection and image guidance** (i.e., Ultrasound) (PRP can only bill for injection 0232T)



# FDA: Regulation of Biologics







# FDA Guidance Documents

Contains Nonbinding Recommendations

## Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

### Guidance for Industry and Food and Drug Administration Staff

*This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.*



# What does this mean for Surgeons?

- Not much...
- Surgeons are free to treat patient using methods they feel is best
- The *practice of medicine* is regulated by *state laws* and the medical licensing boards...*not the FDA*
- The guidance documents represent what a manufacturer (of a Biologic product) is likely to encounter when applying for a license at the FDA



# Summary

- Lots of emerging evidence
- Lots of choices
- Biologics landscape changes quickly
- FDA landscape changes quickly
- Stay updated annually.....





