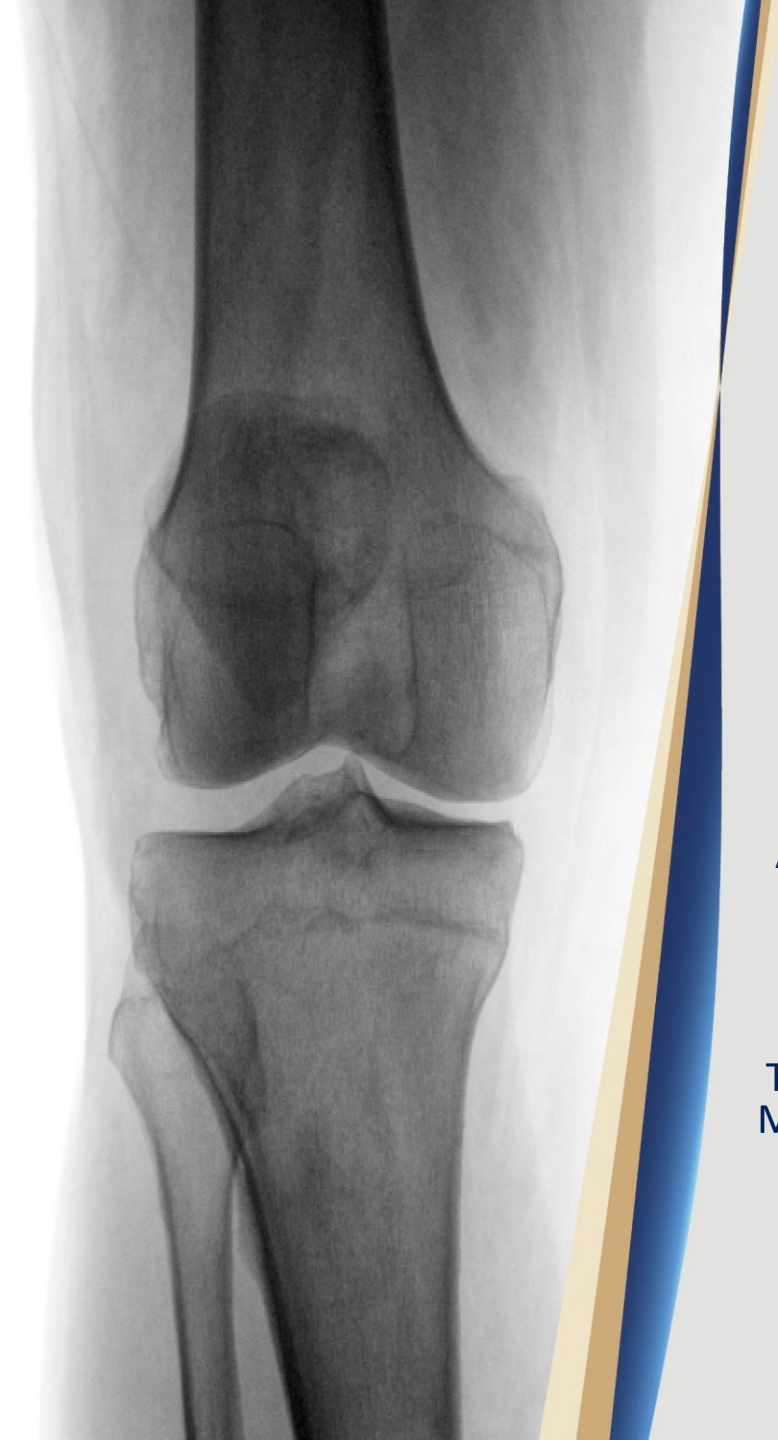

ROTHMAN ORTHOPAEDIC INSTITUTE

Sidney Kimmel Medical College at Thomas Jefferson University

Clinical Efficacy of Intra-articular Mesenchymal Stromal Cells for the Treatment of Knee Osteoarthritis:

A double blinded, prospective, randomized, controlled clinical trial.

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Disclosures

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

- DePuy, A Johnson & Johnson Company: Research support
- GID: Research support
- Johnson & Johnson: Stock or stock Options
- Mitek and DePuy: Paid consultant; Paid presenter or speaker
- Mitek, Knee Creations: Unpaid consultant
- Pacira: Paid consultant; Paid presenter or speaker; Research support

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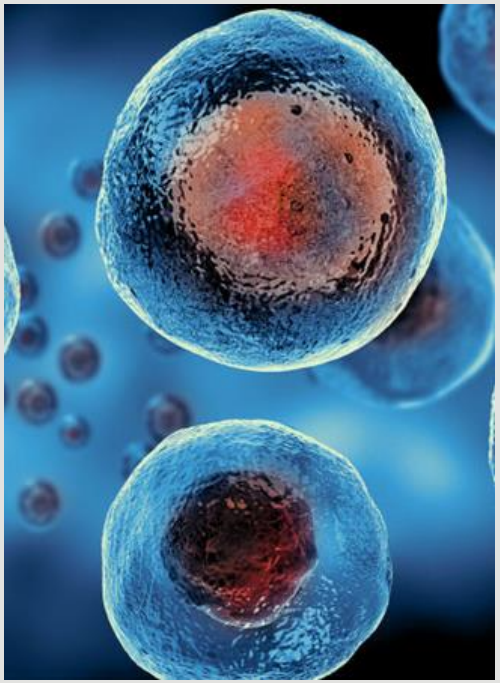
Introduction: Injectable Cell Based Therapy

- Stem cell-based therapies have emerged as possible disease modifying treatments with chondrogenic potential.
- Multiple level 1 studies support the use of isolated stem cells for OA symptoms.[5,6]
  - However, processing isolated stem cells often requires multiple weeks and commercial laboratories.[6]
- Stromal Vascular Fraction (SVF) provides many of the benefits of stem cell therapy without the need for multiple clinic visits or special laboratories.

Introduction: Stromal Vascular Fraction Evidence

- SVF is collected from adipose tissue and consists of a heterogeneous mixture of cells including stromal and vascular progenitor cells.[7]
- Multiple studies have demonstrated the efficacy of SVF for knee OA symptom management.
  - Improve knee OA symptoms for 2-24 months.[8-9]
  - Decrease chondral defect size.[10]
  - Minimal adverse effects.[9]
- However, these results have not been assessed in a randomized, blinded, placebo-controlled trial.



MSC's from Adipose and Bone Marrow

Flow-Cytometry for MSC's

- CD45+ means hematopoietic (blood-derived)
- CD45- means non-hematopoietic (not blood)

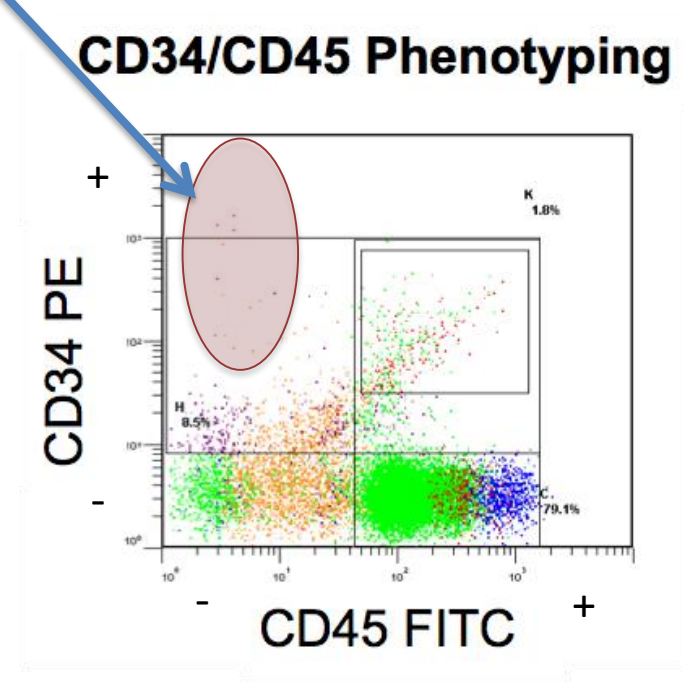
- CD34+ means 'progenitor' (able to proliferate)
- CD34- means non-progenitor (mature, not able to proliferate)

- Target population is CD45-/CD34+
  - Non-hematopoietic progenitor cells
  - Includes the MSC's with other CD45-/CD34+ cells

Flow Cytometry Characterization

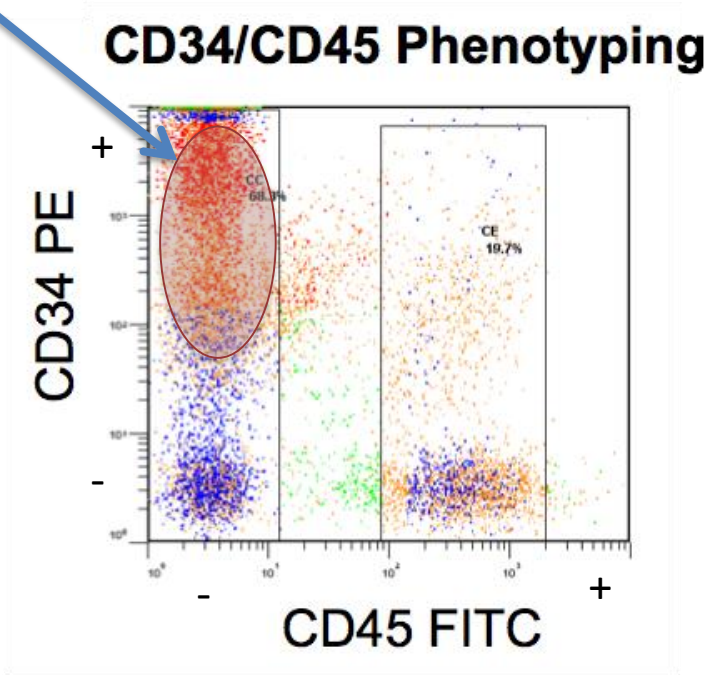
CD45-/CD34+ (MSC's)

CD45-/CD34+



Bone Marrow Aspirate

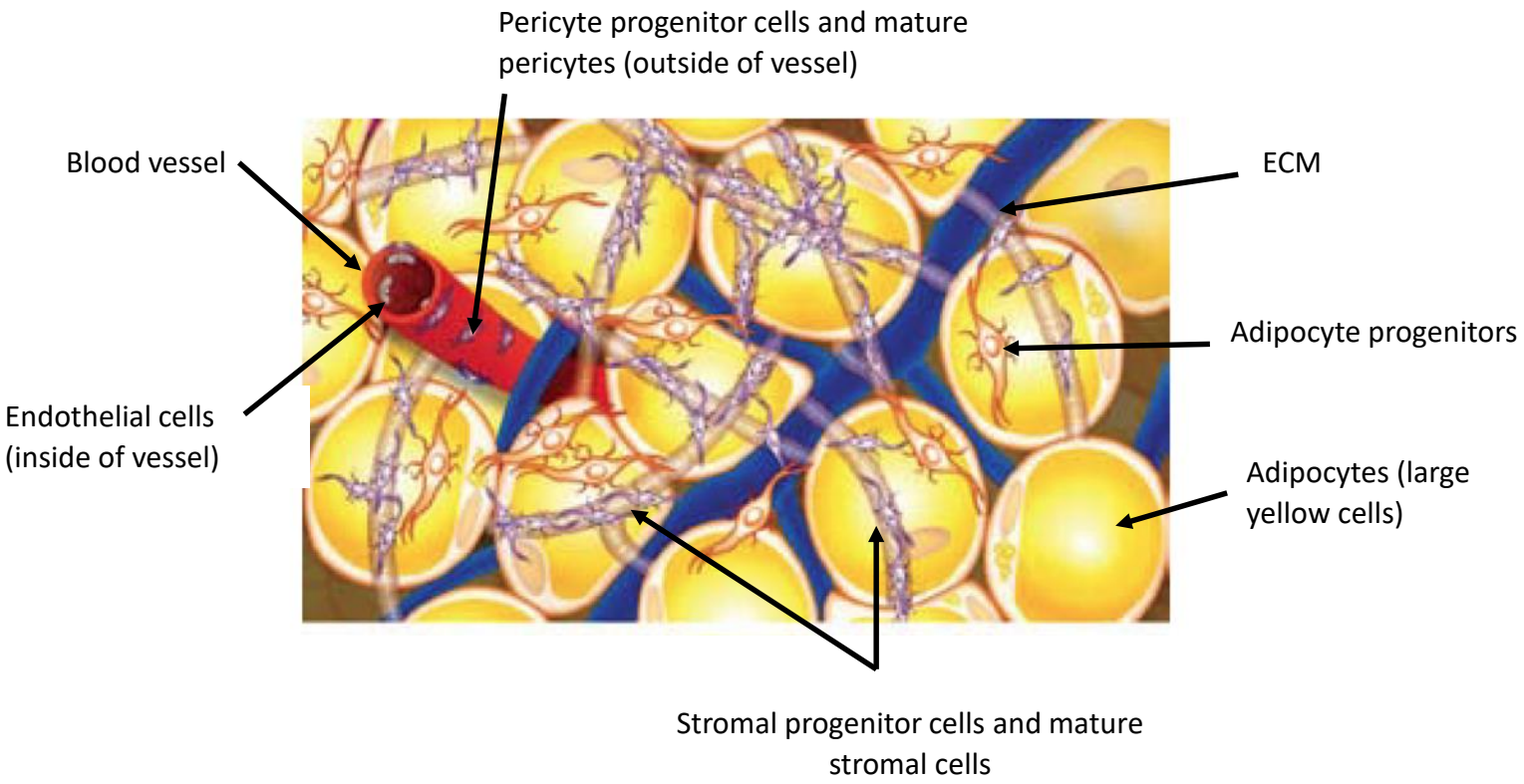
CD45-/CD34+



Adipose SVF

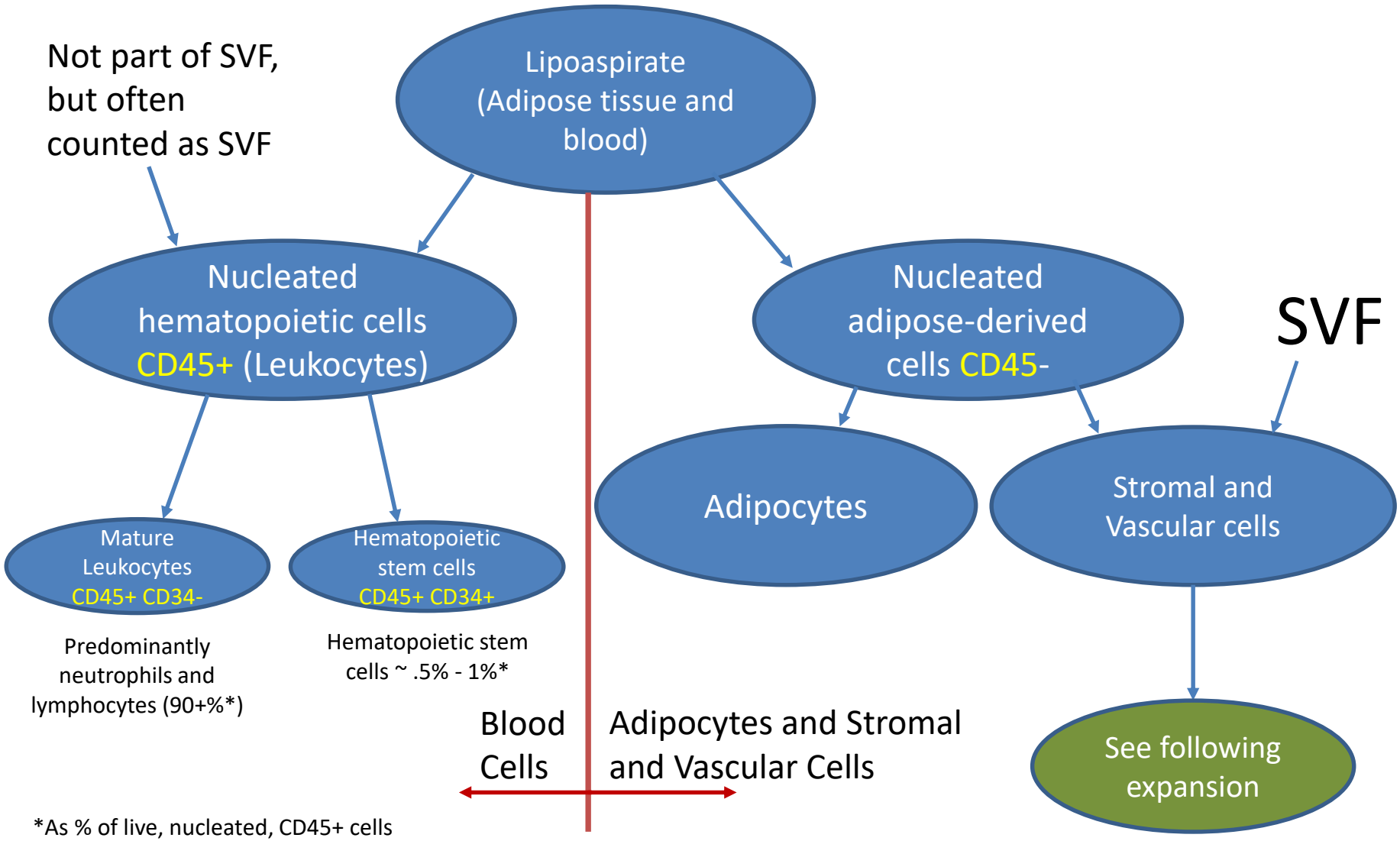
Each colored dot is a nucleated cell

Adipose Tissue Composition



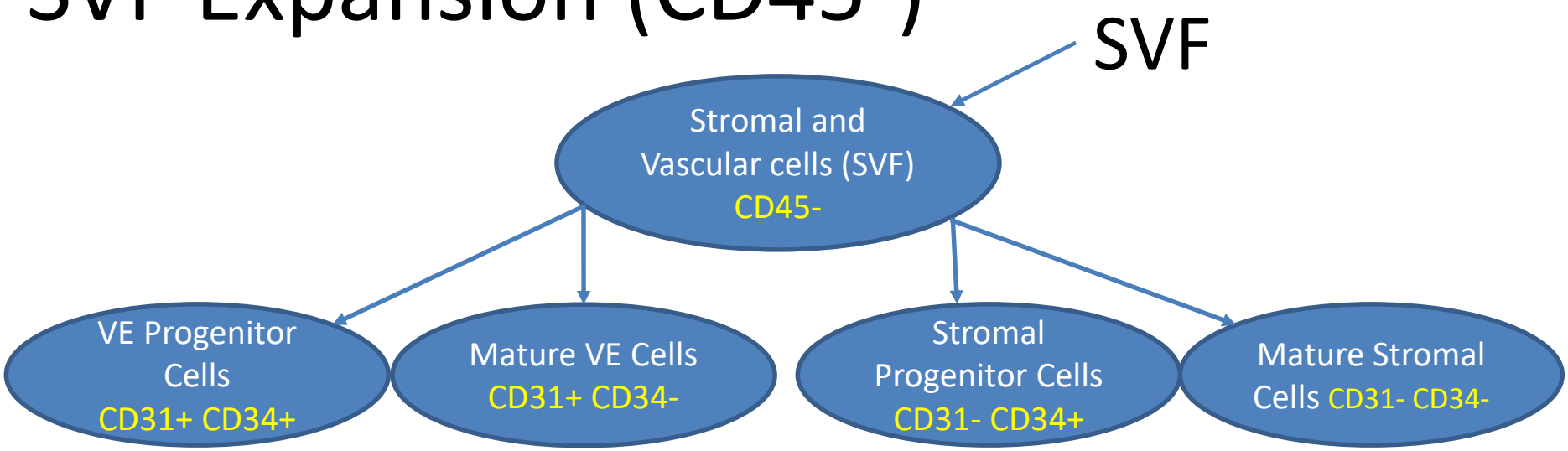
Adapted from Alderman,D, Alexander, R.W.: JOP (2011) Vol. 3

Separation of Lipoaspirate into SVF and Blood Fractions (CD45+ vs CD45-)



*As % of live, nucleated, CD45+ cells

SVF Expansion (CD45-)



(9-12%*)	(9-12%*)	(12-25%*)	(62-75%*)
VEC progenitor	**Mature VEC**	**ASC's (AD MSC's)** **Pericyte progenitors** **Adipocyte progenitors**	**Pericytes** **Fibroblasts/cytes** **M2 macrophages (CD45+)**
Angiogenesis **Reparative/Regenerative**	**Angiogenesis**	**Angiogenesis** **Reparative/Regenerative** • ECM remodeling • Anti-fibrotic • Anti-apoptotic **Immunomodulatory** • Anti-inflammatory • Response regulation • Anti-microbial **Differentiation capacity** **Adipocyte capacity**	**Angiogenesis** **Reparative/Regenerative** • ECM remodeling • Anti-fibrotic • Anti-apoptotic **Immunomodulatory** • Anti-inflammatory • Response regulation • Anti-microbial

*As % of live, nucleated, CD45- cells

Purpose

- Primary Purpose
  - Evaluate the efficacy of intra-articular SVF injections at 6 months, compared to placebo injection.
- Secondary Purpose
  - Evaluate the efficacy of intra-articular SVF injections at 12 months, compared to placebo injection.
  - Evaluate the effects of SVF injections on articular cartilage at 6 and 12 months post injection.

Methods

- Multi-site (3), randomized, double-blinded, placebo-controlled clinical trial.
- A total of 39 patients with symptomatic knee OA were enrolled and randomized to the following groups:
  - High dose SVF: 30 million SVF cells
  - Low dose SVF: 15 million SVF cells
  - Placebo: No cells

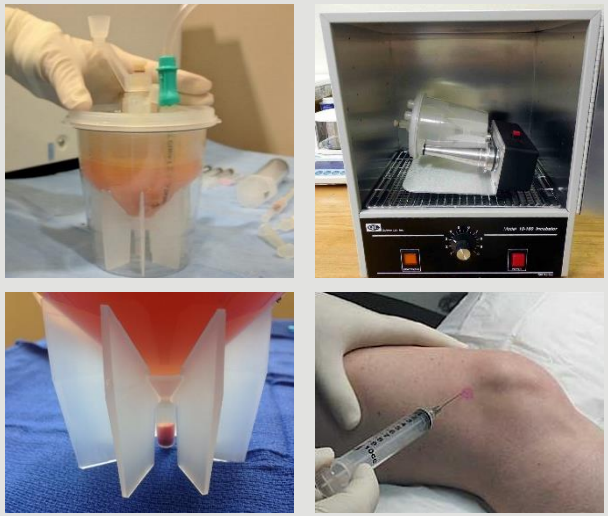
Knee Function and Cartilage Assessment:

- Pre-injection, 6 weeks, 3 months, 6 months 12 months post-injection
  - Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Questionnaire
  - MRI analysis of knee cartilage thickness (Pre-injection, 6 months, 12 months)

SVF Collection, Processing, Injection

SVF cells were collected, processed and injected at the same clinic visit (< 2 hr).

1. Adipose tissue was collected from the abdomen under local anesthetic.
2. The adipose tissue was processed in the GID SVF-2 device under sterile conditions.
3. The appropriate dose was created in a 5 cc syringe and sterilely injected into the knee.
4. Participants were advised to maintain only light activity for the first three weeks after injection.

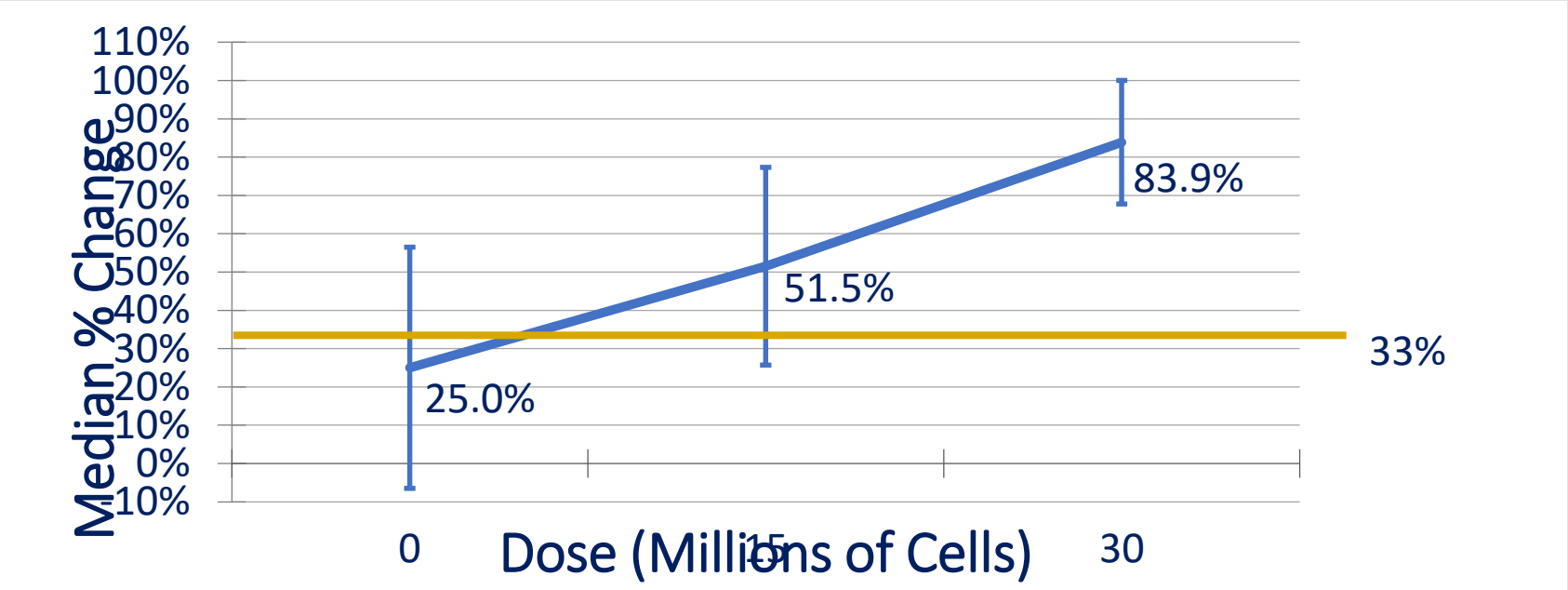


Patient Characteristics

	Treatment Group			
Parameter	Placebo	Low Dose	High Dose	**Total**
Age years	57.1 ± 9.1	60.5 ± 7.9	59.5 ± 11.7	**59.0 ± 9.9**
BMI	27.1 ± 2.7	27.6 ± 4.1	28.8 ± 4.3	**27.8 ± 3.9**
Female % (n)	53.8% (7)	69.2% (9)	46.2% (6)	**56.4% (22)**
Male % (n)	46.2% (6)	30.8% (4)	53.8% (7)	**43.6% (17)**
KL Grade II % (n)	30.8% (4)	30.8% (4)	30.8% (4)	**30.8% (12)**
KL Grade III % (n)	69.2% (9)	69.2% (9)	69.2% (9)	**69.2% (27)**

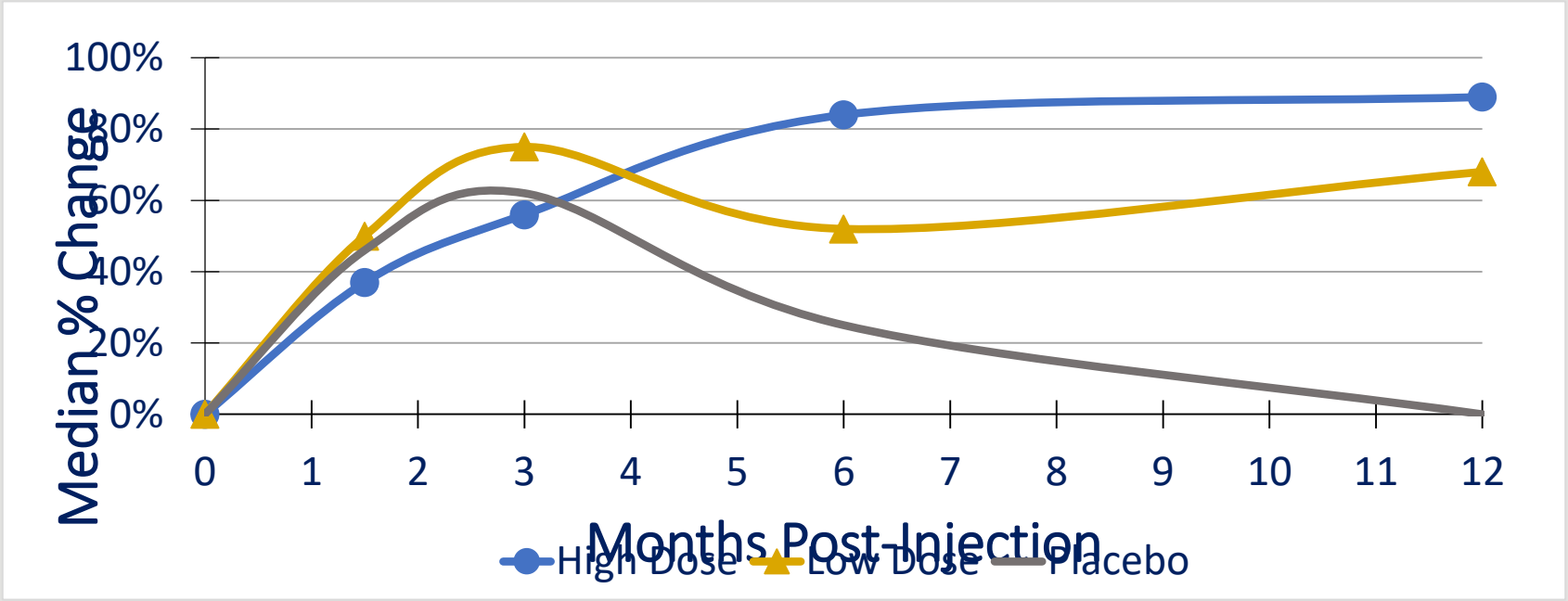
No significant difference in characteristics between treatment groups.

Results: 6-Months Efficacy

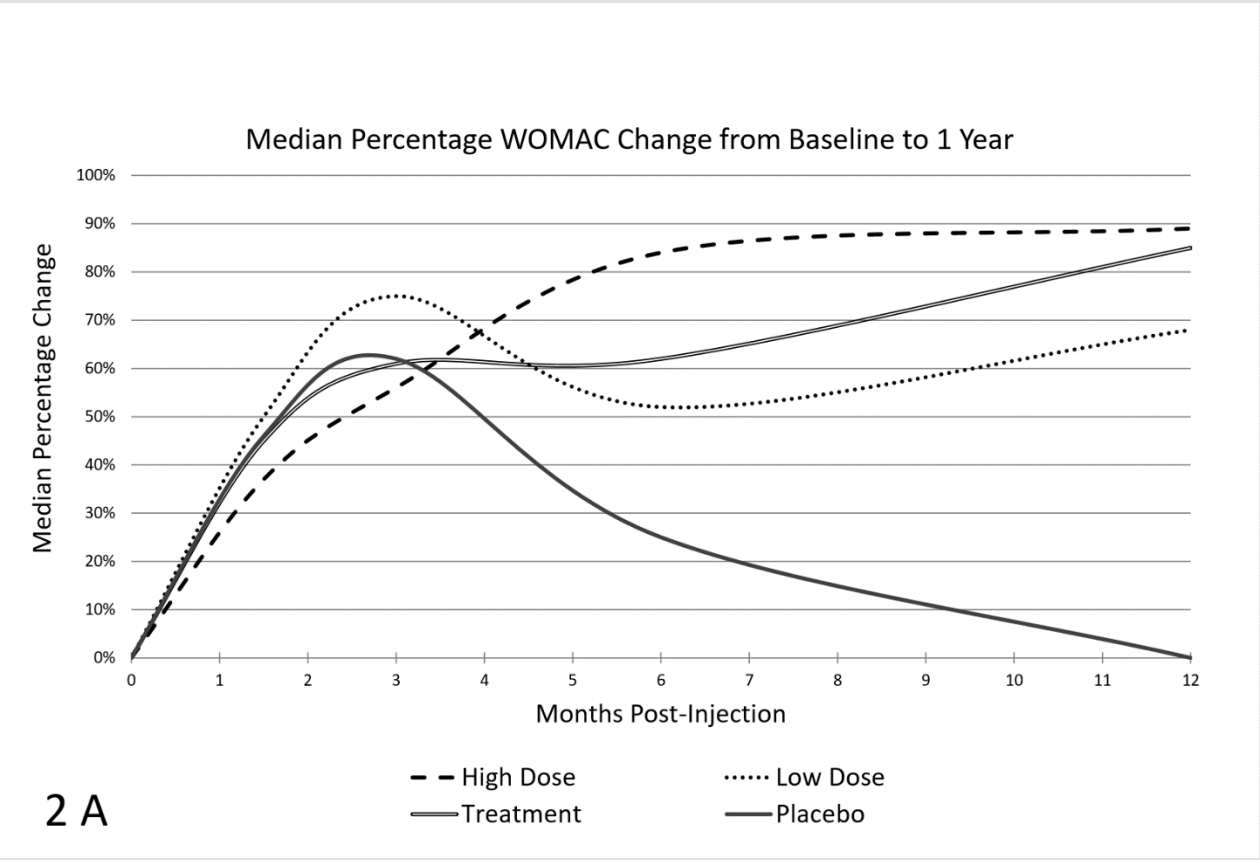


There was a dose dependent improvement in knee OA symptoms 6 months after treatment.

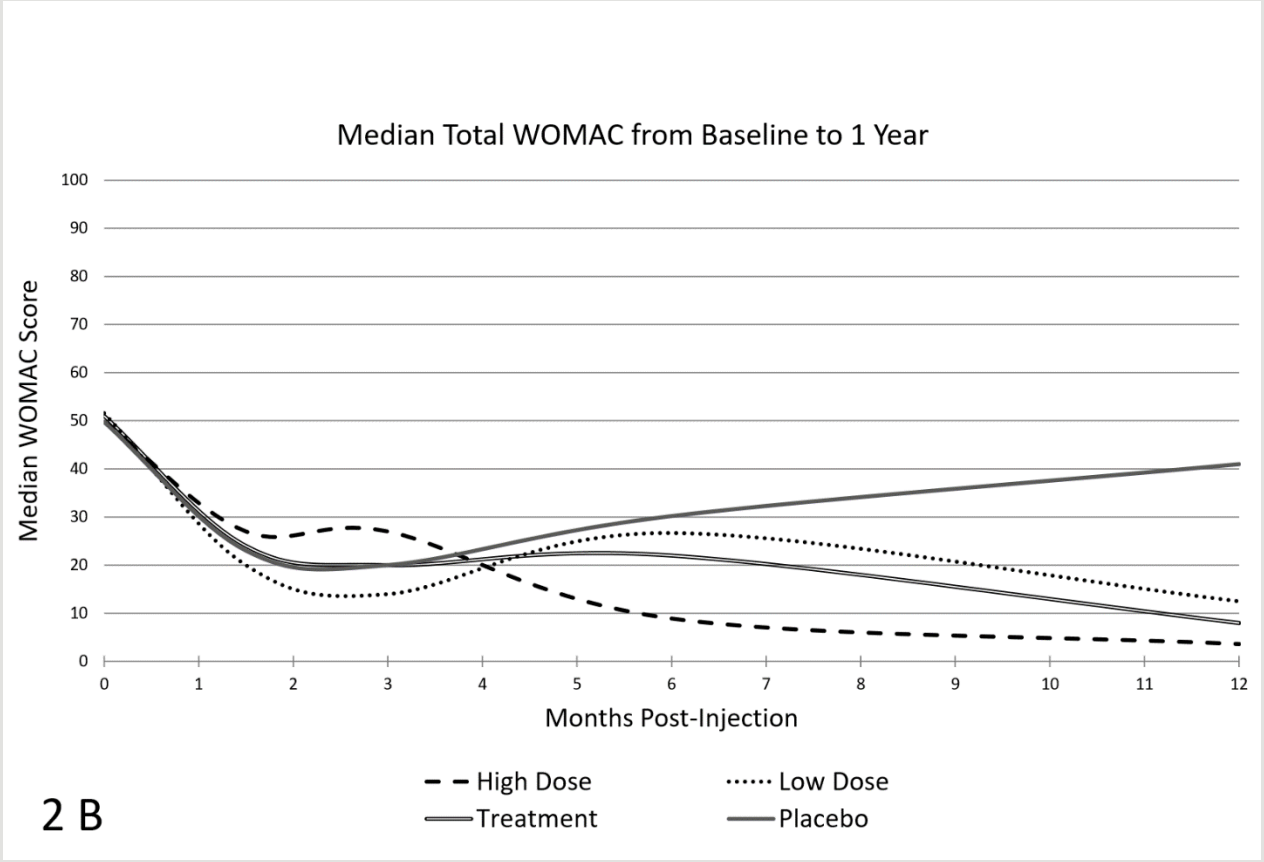
Results: Change in Knee Function Over Time



Both treatment groups experienced significantly better symptom improvement at 6 & 12 months ($p < 0.01$)


Median Percentage WOMAC Change from Baseline to 1 Year
Median Percentage Change
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
9
10
11
12
Months Post-Injection
High Dose
Low Dose
Treatment
Placebo

2 A


Median Total WOMAC from Baseline to 1 Year
Median WOMAC Score
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
12
Months Post-Injection
High Dose
Low Dose
Treatment
Placebo

2 B

Table 4. Changes in Cartilage from Baseline to 6 Months using MRI					
		Cartilage Loss		Outerbridge Classification	
Group	**Number of lesions**	**Baseline Mean (mm)**	**Mean Change at 6 months (mm)**	**Baseline Median (range)**	**Median Change at 6 Months**
All subjects	60	12.6	0	3 (1 – 4)	0
Treatment Group	46	11.5	-0.2	3 (1 – 4)	0
Placebo Group	14	16.3	0.5	4 (1 – 4)	0
Responders (>MCID)	38	13.2	0.2	3 (1 – 4)	0
Non-responders (<MCID)	22	11.6	-0.4	3 (1 – 4)	0
MCID: Minimal Clinically Important Difference					

Results: Cartilage and Adverse Effects

- At 6 month and 1 year follow-up, there was no visible quantifiable changes in knee cartilage thickness by MRI.
  - No significant difference between groups.
- At 1 year follow-up there were there were no signs of:
  - heterotopic ossification
  - neoplastic growth (benign or malignant)
- No serious adverse effects were reported.
  - One patient experienced aseptic knee swelling after a high dose SVF injection.

Conclusion

- SVF cells can be collected, processed and injected intra-articularly at one clinic visit.
- SVF injections are relatively safe with minimal adverse effects.
- SVF injections can significantly decrease knee OA symptoms and pain at 6 months and 1 year, compared to placebo.
- SVF injections can delay progression to the need for TKA or potentially provide an alternative to TKA.
- The primary effects of SVF on articular cartilage are yet to be quantified.

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Osteochondral Transplant

- Fresh Allograft
  - Garrett
    - 94% good & excellent, 17 patients, femoral OCD's, 3.2 yrs
  - Bugbee et al
    - 79% good & excellent, 69 patients, femoral OCD's, 5.2 yrs
  - Gross et al, femoral traumatic lesions
    - 95% survival 5yrs, 85% survival 10yrs

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Osteochondral Allograft

- Pros
  - Bone to bone healing
  - Hyaline cartilage viability
  - No donor sites issues
  - Composite graft
  - Salvage option
- Cons
  - Sizing
  - Procurement
  - Availability
  - High cost
  - Disease transmission
  - Immunologic issues
  - Durability
  - “Burn bridges”

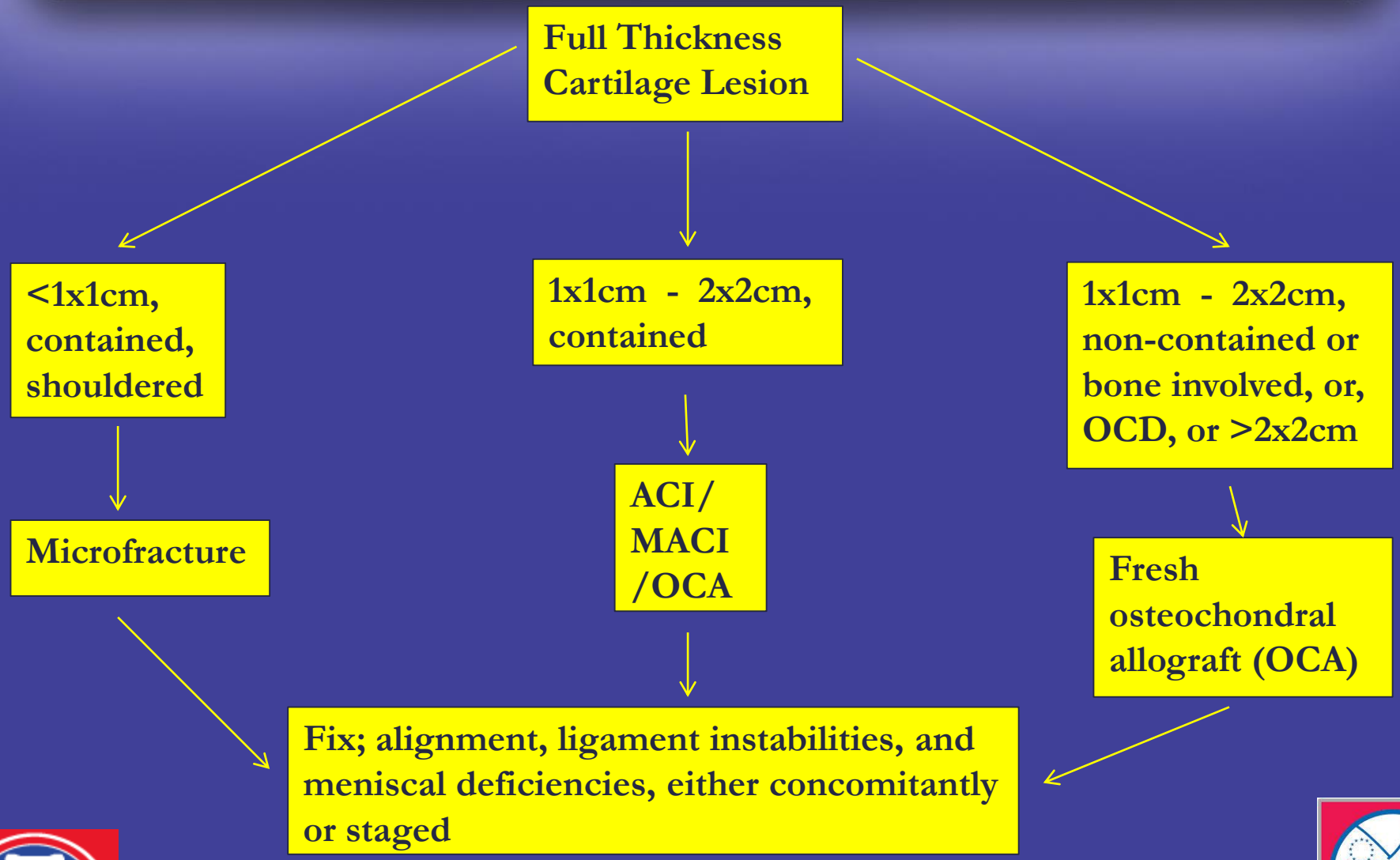
Summary

- Full thickness articular cartilage defects can be repaired with multiple different techniques
  - All showing significant improvement in outcomes
  - No consensus on which technique is superior

My Thoughts

- **Make a Mental Checklist for chondral lesion:**
  - **Size:**
    - **Smaller better, Larger worse**
  - **Location:**
    - **Higher contact area worse then low contact area**
  - **Containment:**
    - **Contained better then non-contained**
  - **Shoulders:**
    - **Shouldered better then non-shouldered**
  - **Bone involvement and depth of involvement:**
    - **Edema, cysts, surface osteophytes, OCD**
  - **Patient H&P**
    - **Age, activity, expectations, traumatic vs degenerative**
    - **Alignment and ligament stability**

My Thoughts


Full Thickness Cartilage Lesion
<1x1cm, contained, shouldered
1x1cm - 2x2cm, contained
1x1cm - 2x2cm, non-contained or bone involved, or, OCD, or >2x2cm
Microfracture
ACI/ MACI /OCA
Fresh osteochondral allograft (OCA)
Fix; alignment, ligament instabilities, and meniscal deficiencies, either concomitantly or staged

THANK YOU.

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