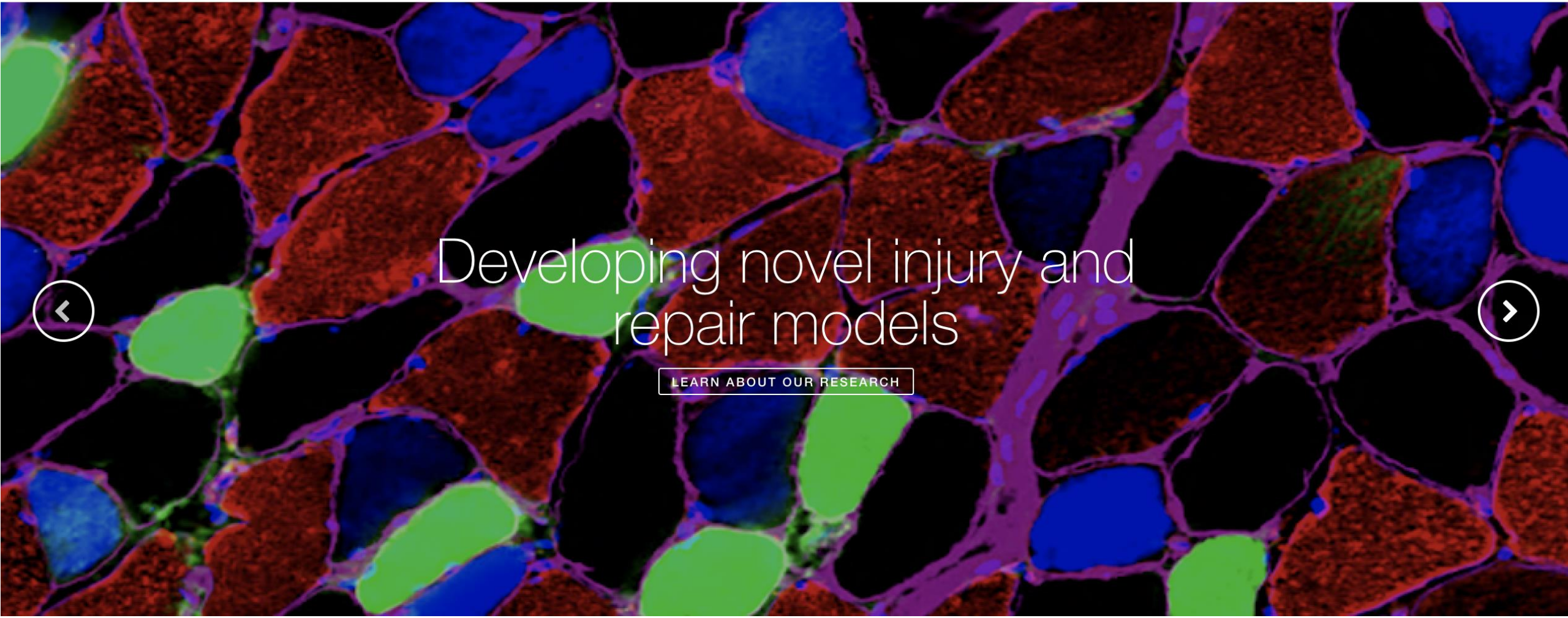
Biologic Treatments for MSK Conditions
PT/ATC Sports Conference
2022

Brian Feeley, MD
Chief, Sports Medicine and Shoulder Surgery

Disclosures

- Consultant—Bioniks, Kaliber
- Research—NIH, Orthofix, VA Healthcare, Stryker
- Editorial-JSES, CRMSM, JOR
- Advisory Boards—NFL

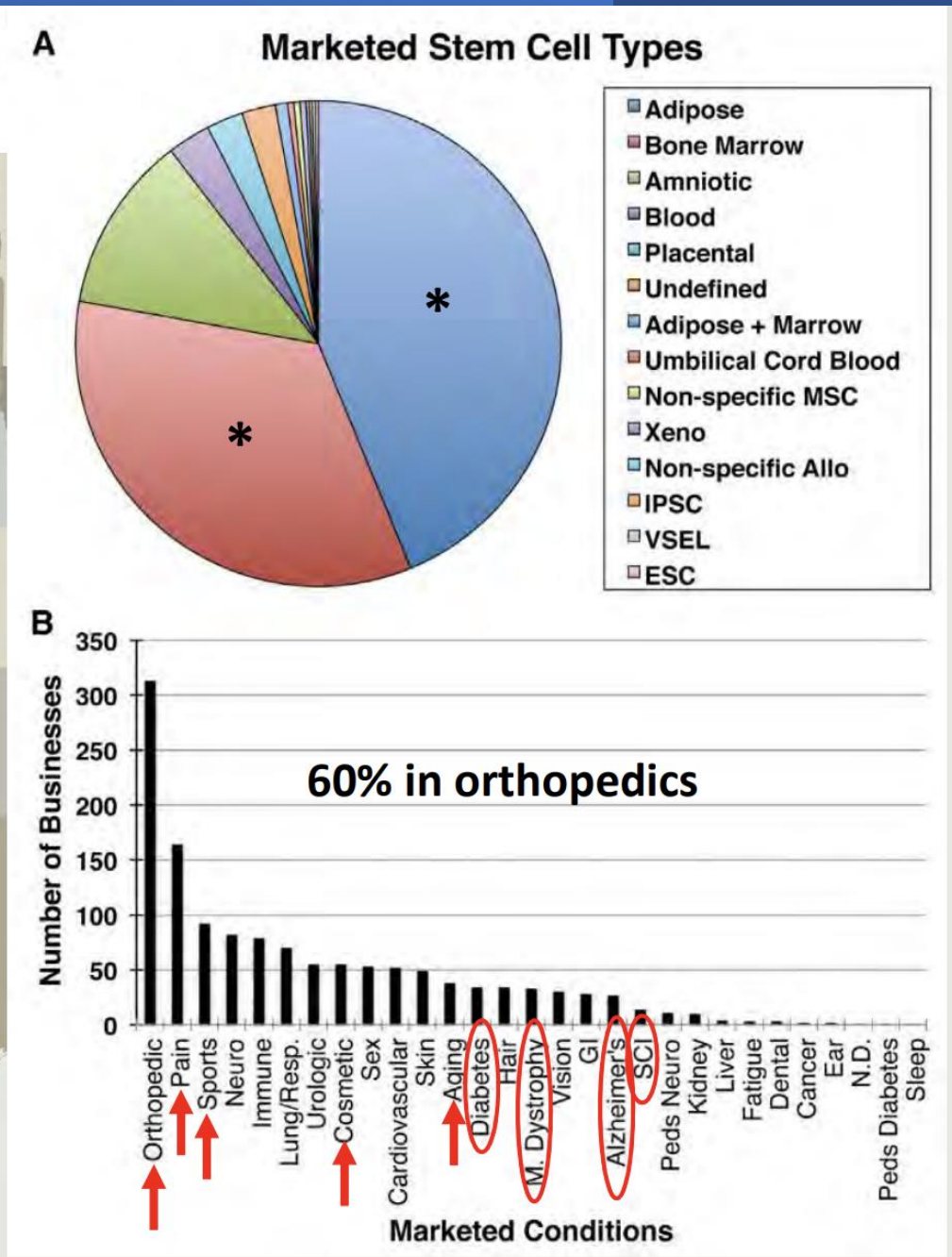

Developing novel injury and repair models
LEARN ABOUT OUR RESEARCH

Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry

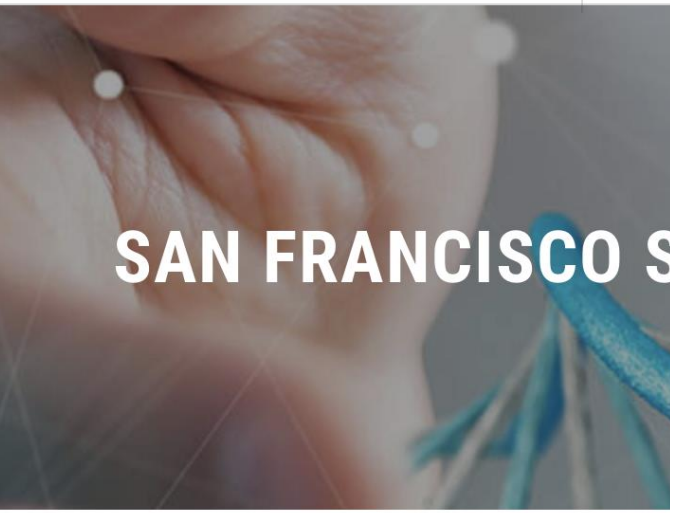
Leigh Turner[1,*] and Paul Knoepfler[2,3,*]

State	N
California	113
Florida	104
Texas	71
Colorado	37
Arizona	36
New York	21

Hotspot Cities	N
Beverley Hills	18
NYC	14
San Antonio	13
Los Angeles	12
Austin	11
Scottsdale	11
Phoenix	10



ADVANCED STEM CELL INSTITUTE

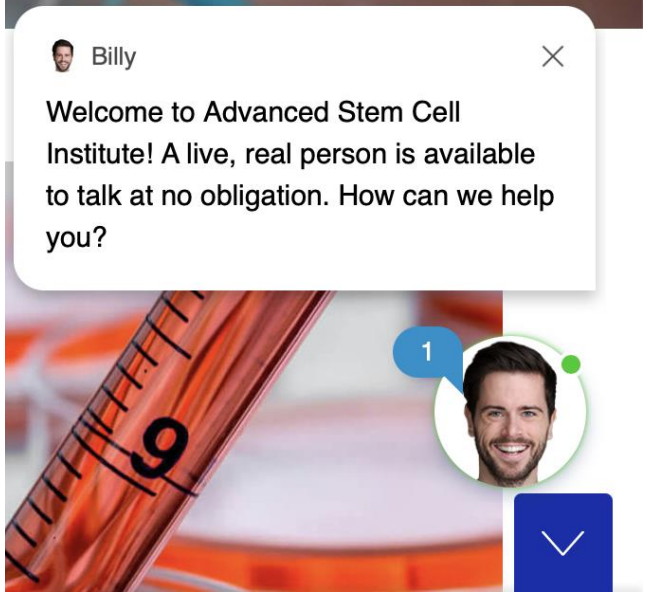


Stem Cell Injection Thera
California

Problems with the knees are so commo
arthroscopic knee surgery in the U.S. alc
is a surgical procedure in which a docto
while looking through an invasive instru
requires general or spinal anesthesia, ar

I am writing this review because I am excited. After 2 years and over 10 doctors, I can finally say my shoulder feels great. I was diagnosed with shoulder rotator cuff tear. I had cortisone shots, and therapy without significant improvement. My orthopedic surgeon insisted that surgery is my only option. Knowing some people who have done this surgery and their mediocre results I didn't feel comfortable with the idea of surgery. On researching the web I found that stem cells are helpful. I educated myself and consulted the doctors at Advamced Stem Cell Institute. The Dr spent a lot of time explaining my options, and show stem cells can help me avoid surgery. He reviewed my MRI and I scheduled he procedure. I have to say that their prices are very competitive, as I shopped around several other offices anywhere from $4,500-$. 6,500. I paid only $3,500 and it was the best investment. Now 4 months later I am playing baseball with my son again . If you were offered surgery, look into stem cells.

ICS SUCCESS STORIES **CONTACT**

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Back of hands & arms
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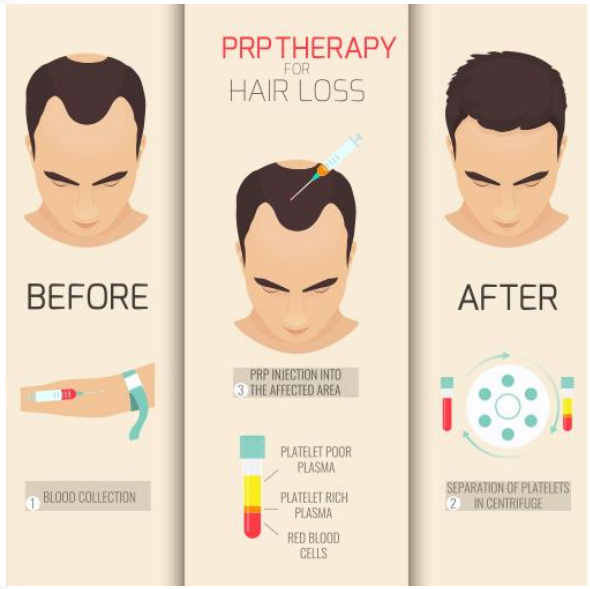
Chest & decolletage


PRP THERAPY
FOR
HAIR LOSS
BEFORE
AFTER
PRP INJECTION INTO THE AFFECTED AREA
3
PLATELET POOR PLASMA
PLATELET RICH PLASMA
RED BLOOD CELLS
1 BLOOD COLLECTION
2 SEPARATION OF PLATELETS IN CENTRIFUGE

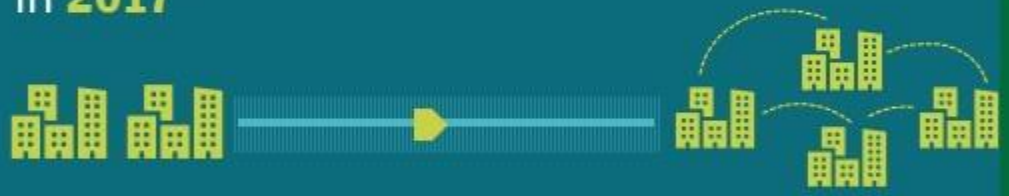

Better Self-Image
WITH PLATELET-RICH PLASMA

The market will be **ACCELERATING** growing at a **CAGR** of nearly **11%**

INCREMENTAL GROWTH **$820 mn**

The year-over-year growth rate for **2018** is estimated at **10.50%**

The **AUTOLOGOUS TRANSPLANTS SEGMENT** occupied **HIGHEST** market share in **2017**



53% of the growth will come from the **AMERICAS**

One of the **KEY DRIVERS** for this market will be the increase in awareness of stem cell therapy

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GLOBAL STEM CELL THERAPY MARKET 2018-2022

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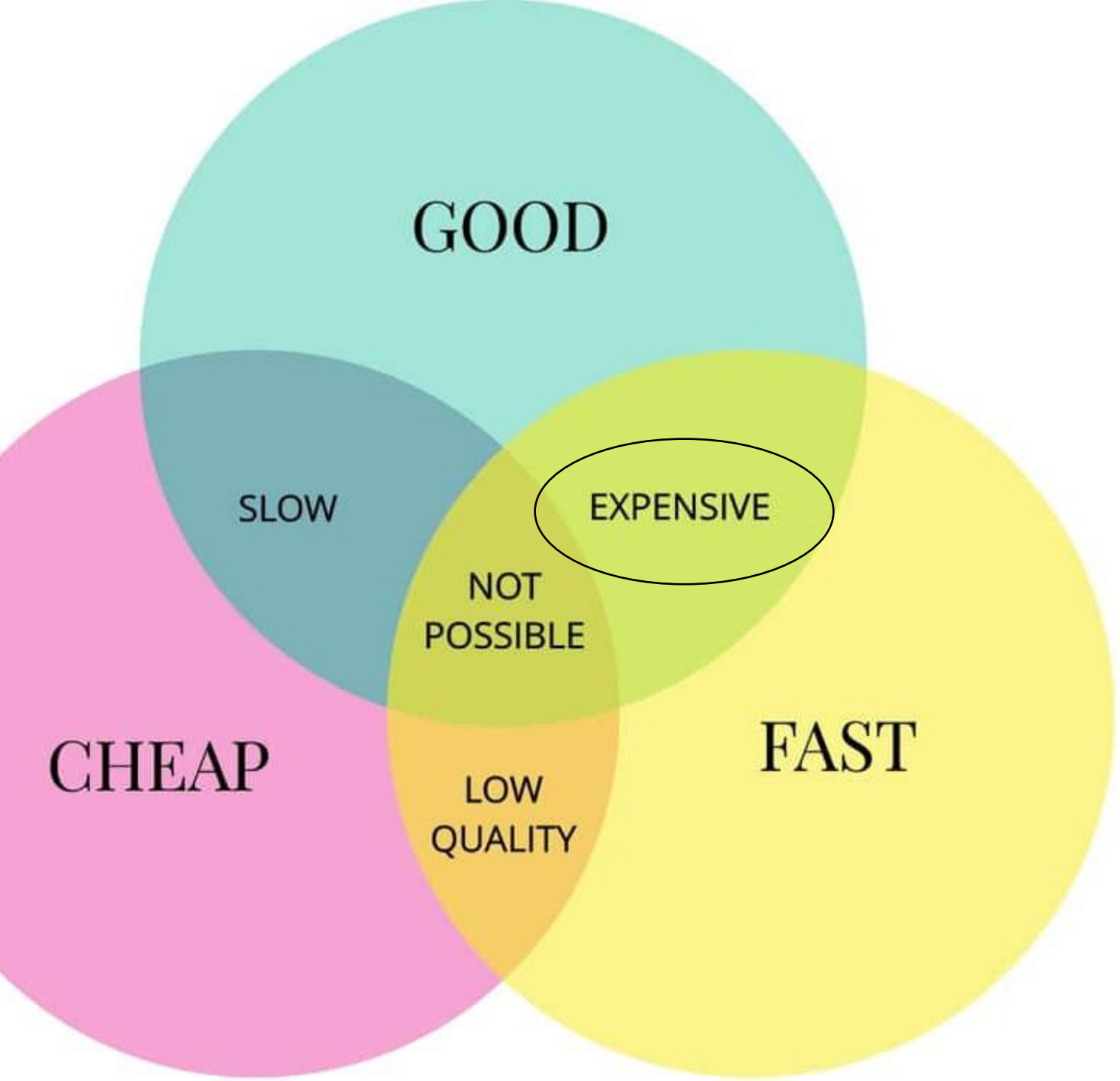
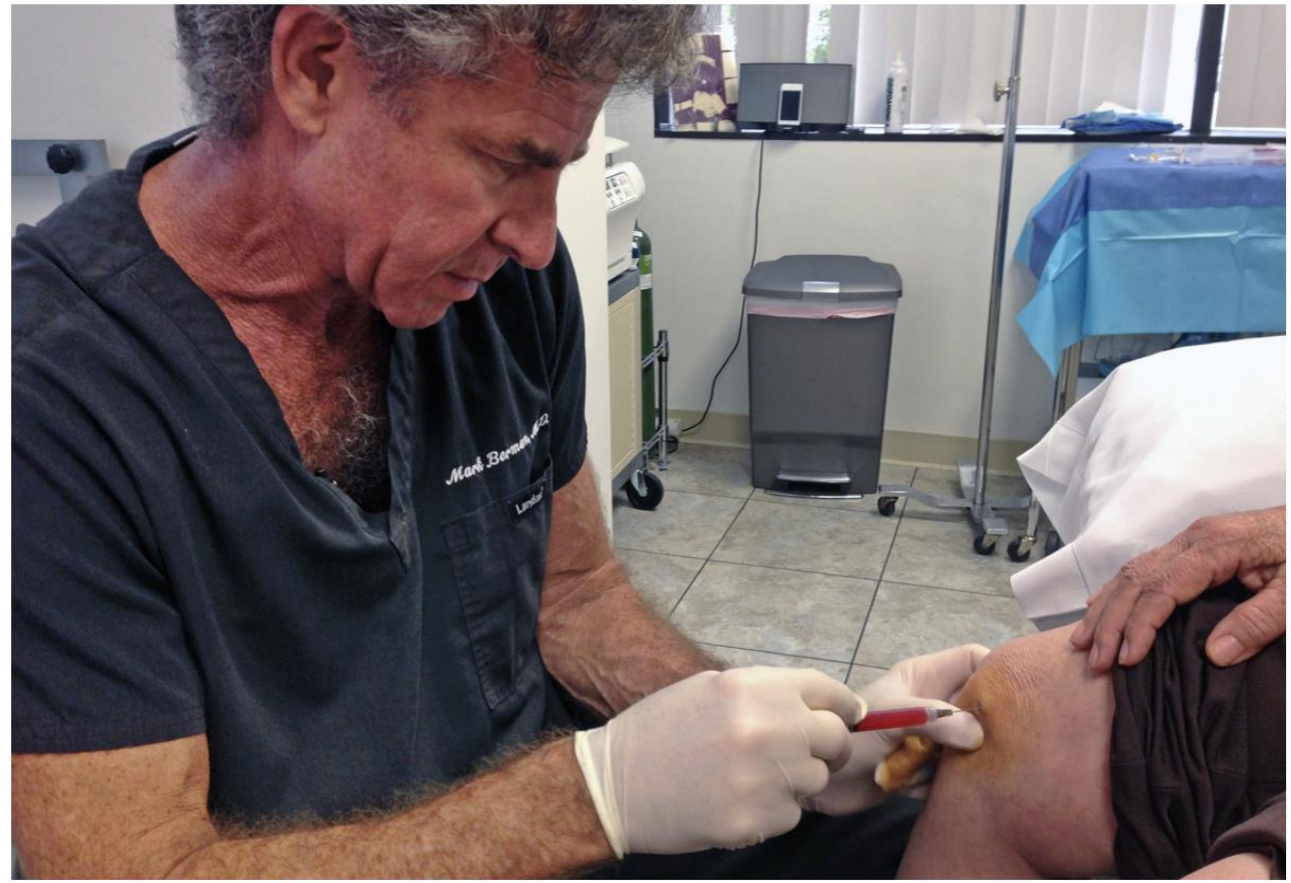


How Do You Figure Out What a Stem Cell Procedure Should Cost?

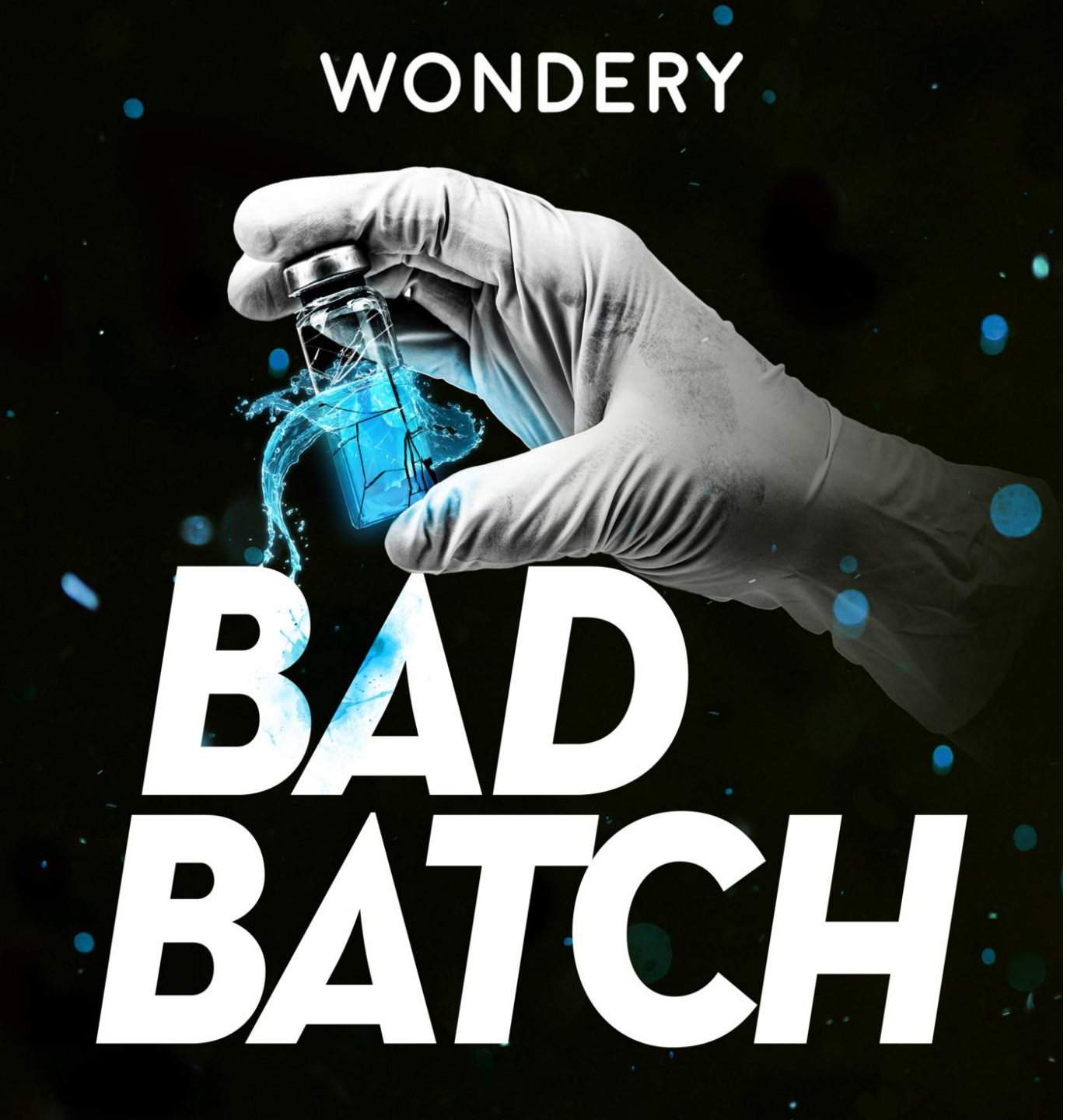
Regenexx

12 People Hospitalized With Infections From Stem Cell Shots

F.D.A. Moves to Stop Rogue Clinics From Using Unapproved Stem Cell Therapies



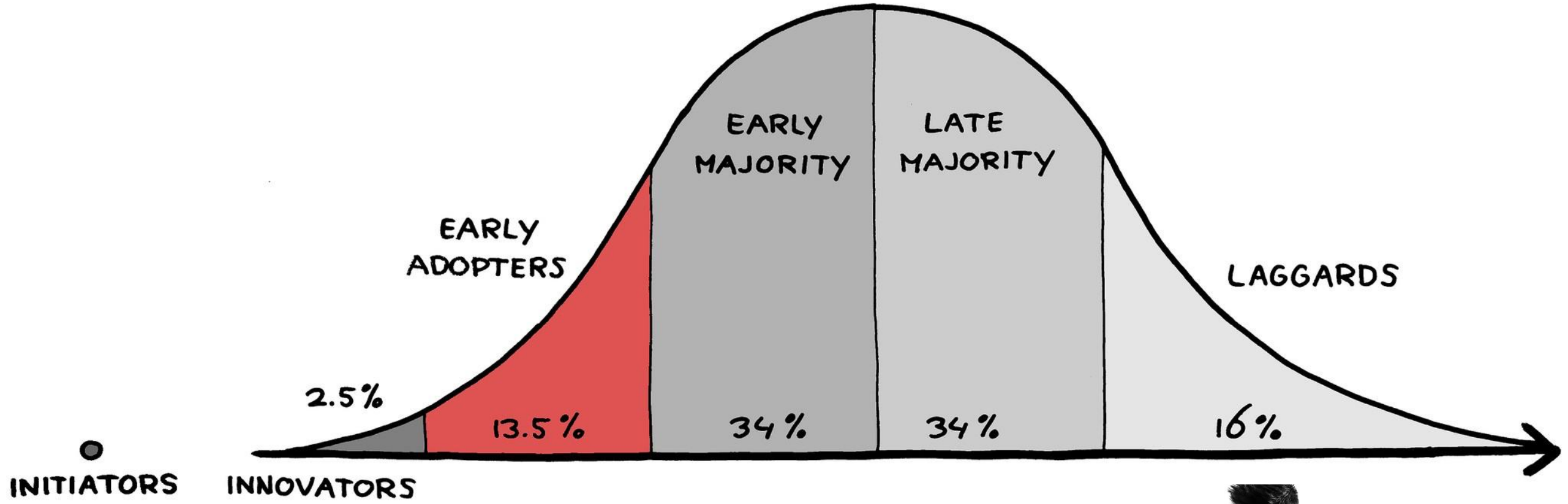
Dr. Mark Berman, of the Cell Surgical Network, in 2014 at his practice in Beverly Hills. Dr. Berman is a founder of the California Stem Cell Treatment Centers, where patients received an unapproved stem cell treatment made with the help of a smallpox vaccine and other ingredients. Raquel Maria Dillon/Associated Press



Harvard Calls for Retraction of Dozens of Studies by Noted Cardiac Researcher

Some 31 studies by Dr. Piero Anversa contain fabricated or falsified data, officials concluded. Dr. Anversa popularized the idea of stem cell treatment for damaged hearts.

Dr. Piero Anversa, affiliated with the Harvard Medical School, above, and Brigham and Women's Hospital in Boston, departed in 2015 following questions about his research.


EARLY MAJORITY
LATE MAJORITY
EARLY ADOPTERS
LAGGARDS
2.5%
13.5%
34%
34%
16%
INITIATORS
INNOVATORS


Should we be surgically injecting torn ACLs with stem cells?
Regenexx®


ALTERNATIVES TO SURGERY
Using Your Own Stem Cells to Heal Your Body
Regenexx®
Tampa Bay
The Orthopedic Stem Cell Experts

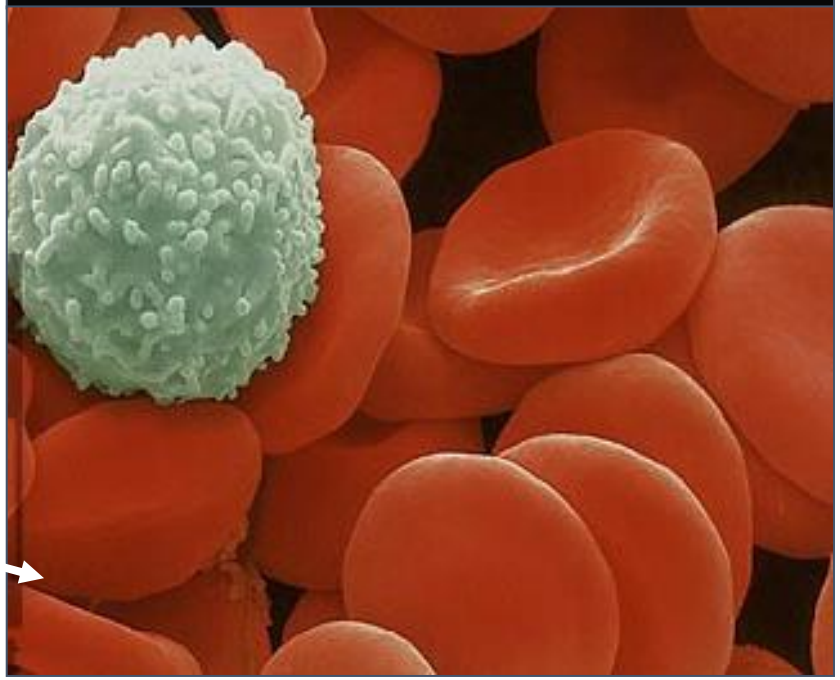
What would PRP or stem cells work for?

- **Cartilage regeneration**
  - *Knee osteoarthritis*
- **Tendonopathy/tendon to bone healing**
  - *Rotator cuff tears*
  - *Tennis elbow, achilles tendonopathy*

What is PRP?

Platelet Rich Plasma: "Volume of plasma that has a platelet count above the baseline of whole blood."

Plasma and platelets



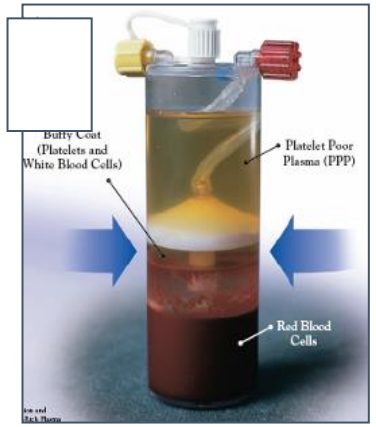
+/-WBC's

-RBC's

All PRPs are NOT the same!

Magellan™ Medtronic

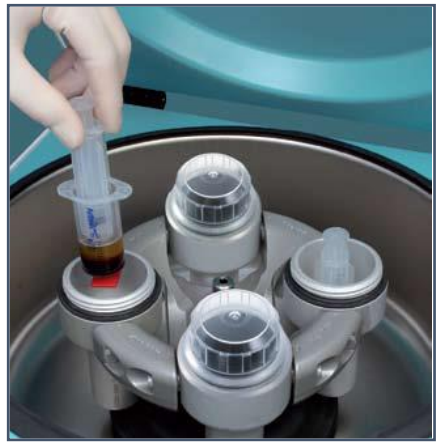
Caption™
Smith & Nephew



GPS®III Biomet

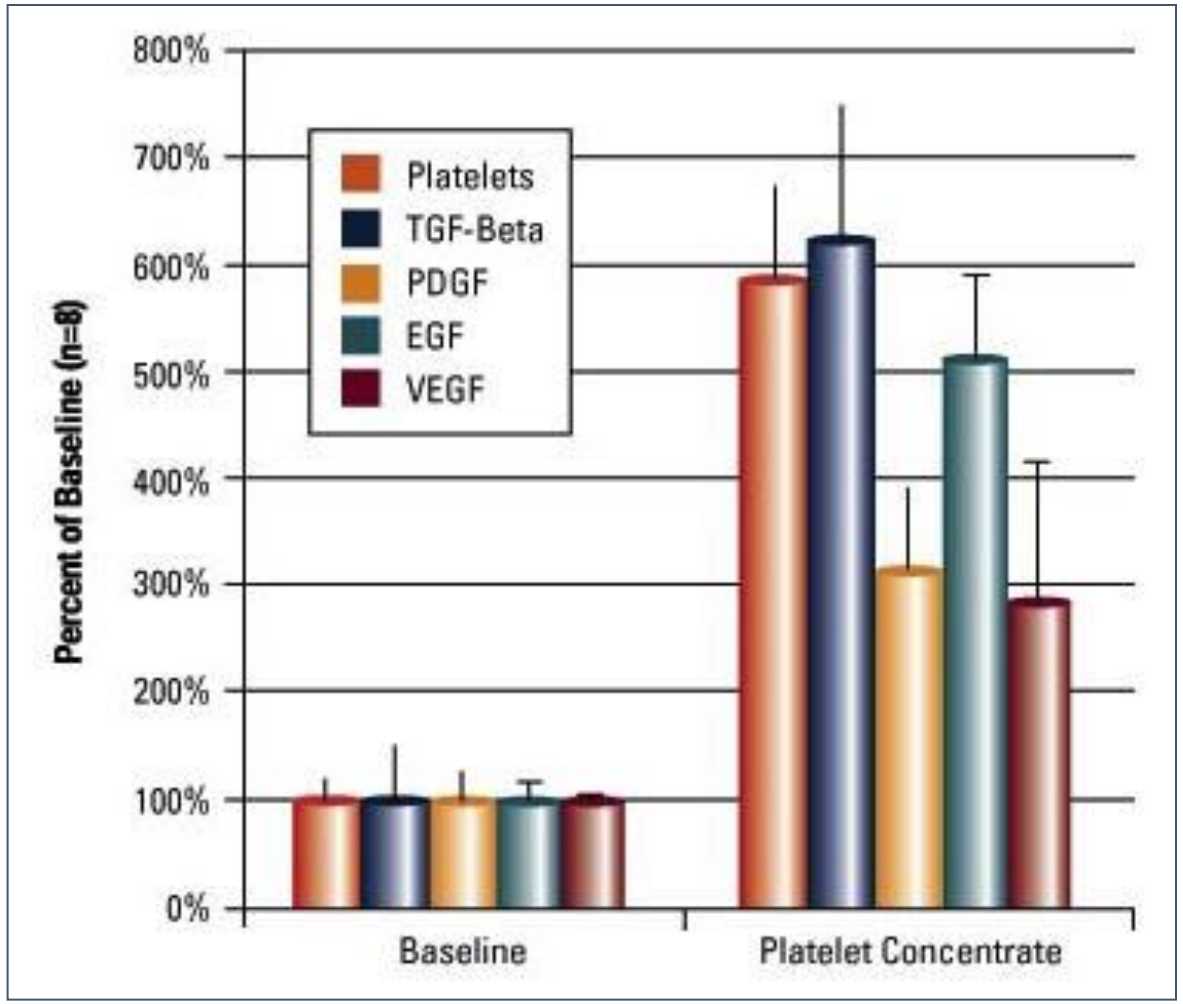
Symphony II™ DePuy

Cascade™ MTF



Arthrex ACP™

PRP releases potent growth factors



Platelet-membrane-based

- **1100 proteins**
- **The Good:**

TGF-B – Transforming growth factor
PDGF – Platelet derived growth factor
IGF – Insulin-like growth factor
FGF – Fibroblast growth factor
VEGF – Vascular endothelial growth factor
Cell-adhesion molecules – fibronectin, fibrin, vitronectin

Not so good
Growth factor inhibitors…they are there too

But the actual amount is not consistent…

Final platelet and growth factor concentration dependent upon:

- **Amount of whole blood used**
- **Efficacy of platelet recovery**
- **Final volume of plasma in which the platelets are suspended.**

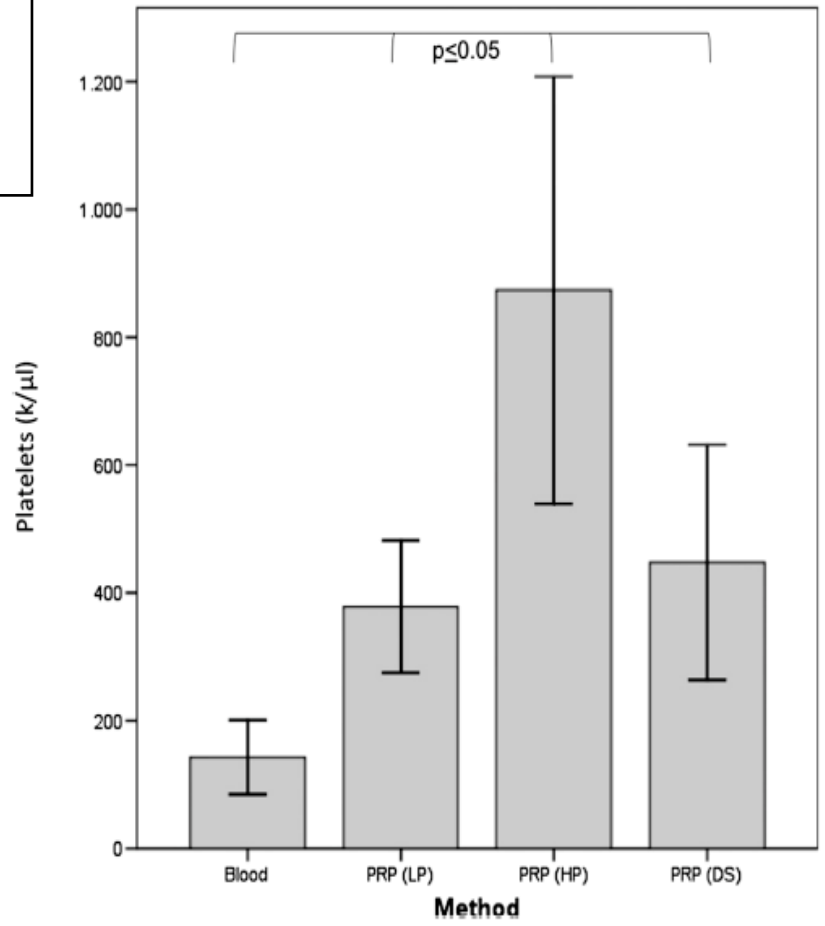
…and PRP can vary from day to day in the *same individual.*

Platelet-Rich Plasma Differs According to Preparation Method and Human Variability

Augustus D. Mazzocca, MS, MD, Mary Beth R. McCarthy, BS, David M. Chowaniec, BS, Mark P. Cote, DPT, Anthony A. Romeo, MD, James P. Bradley, MD, Robert A. Arciero, MD, and Knut Beitzel, MD

Investigation performed at the Department of Orthopaedic Surgery, University of Connecticut Health Center, Farmington, Connecticut

- 8 subjects
  - Mean age 31.6 years
  - 3 repetitive blood draws
- Conclusions
  - PRP > whole blood in plt conc
  - Single = Double spin techniques
  - High variability within systems



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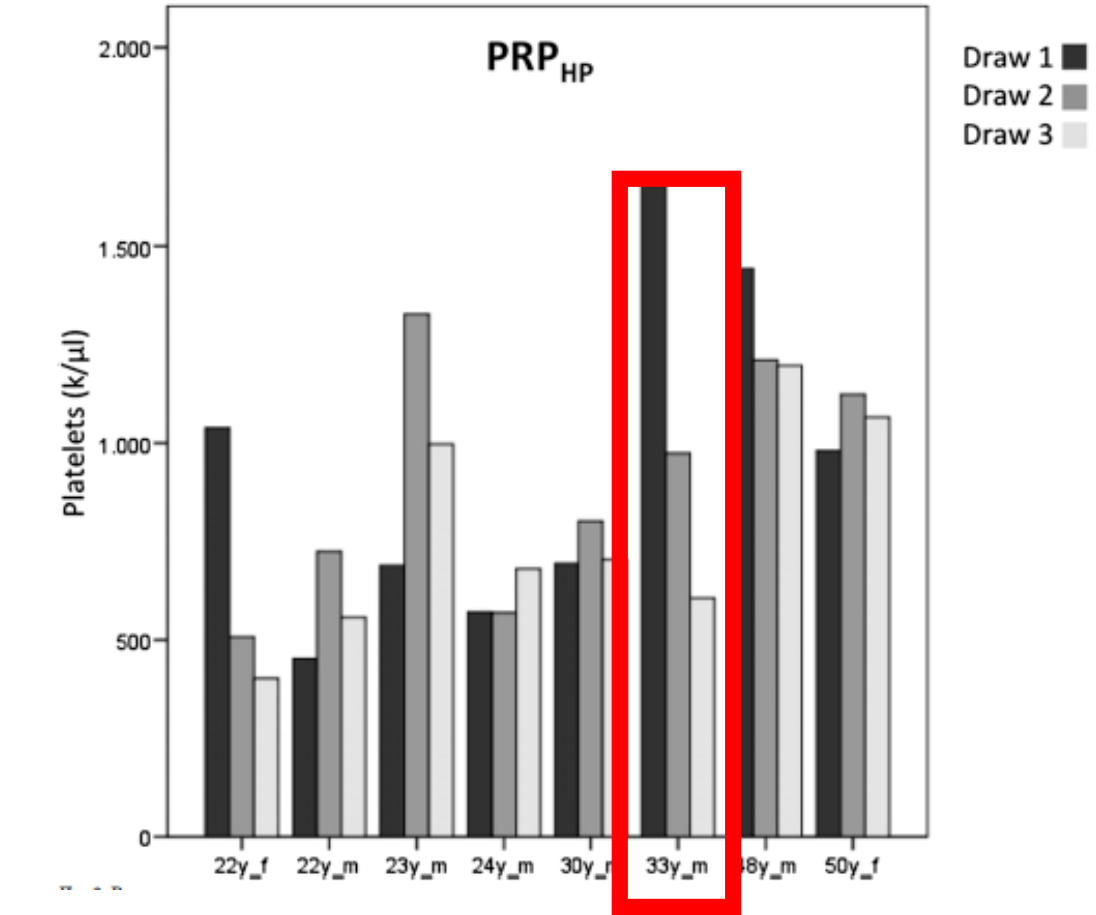
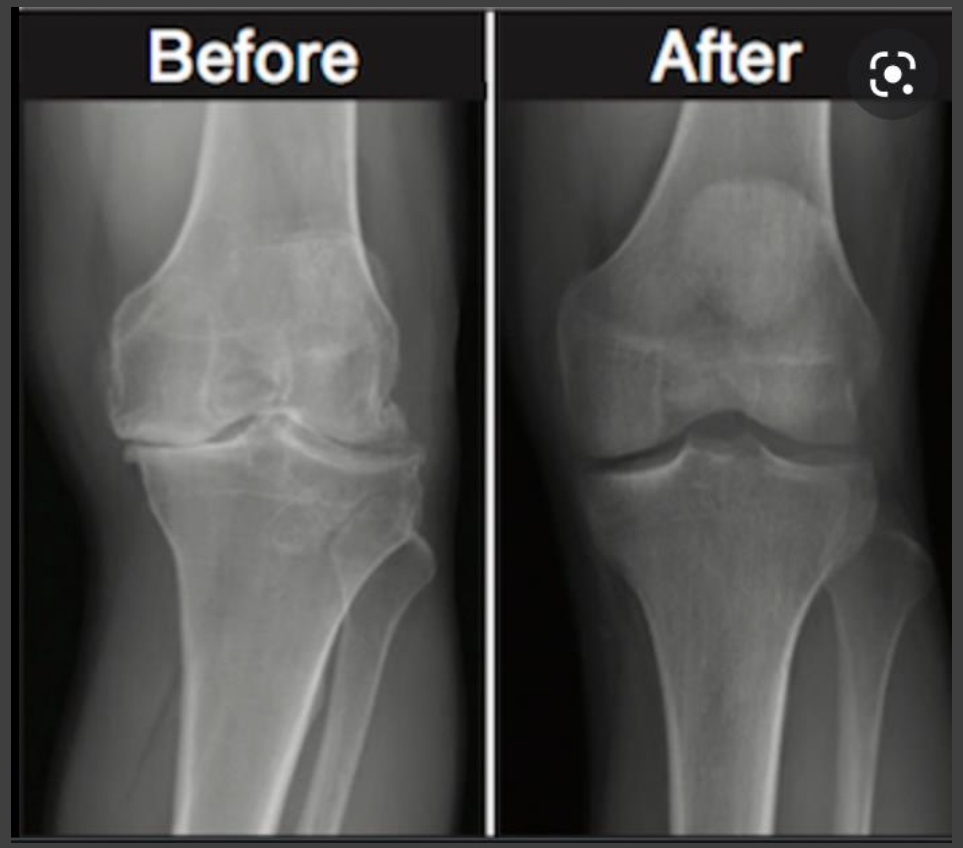


- Cell counts inconsistent day to day
- *Has implications since PRP is often given repetitively*
- *Biologic factors that may influence this variability unknown*

Hilton Head Island Stem Cell Therapy Fraum Chiropractic Life Center



Will PRP work for my aching knee?

Hyaluronic Acid Versus Platelet-Rich Plasma

A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis

Brian J. Cole,*†‡§||¶ MD, MBA, Vasili Karas,# MD, MS, Kristen Hussey,† MS, Kyle Pilz,†¶ MMS, PA-C, and Lisa A. Fortier,** DVM, PhD, DACVS
Investigation performed at the Rush University Medical Center, Chic

AJSM 2017

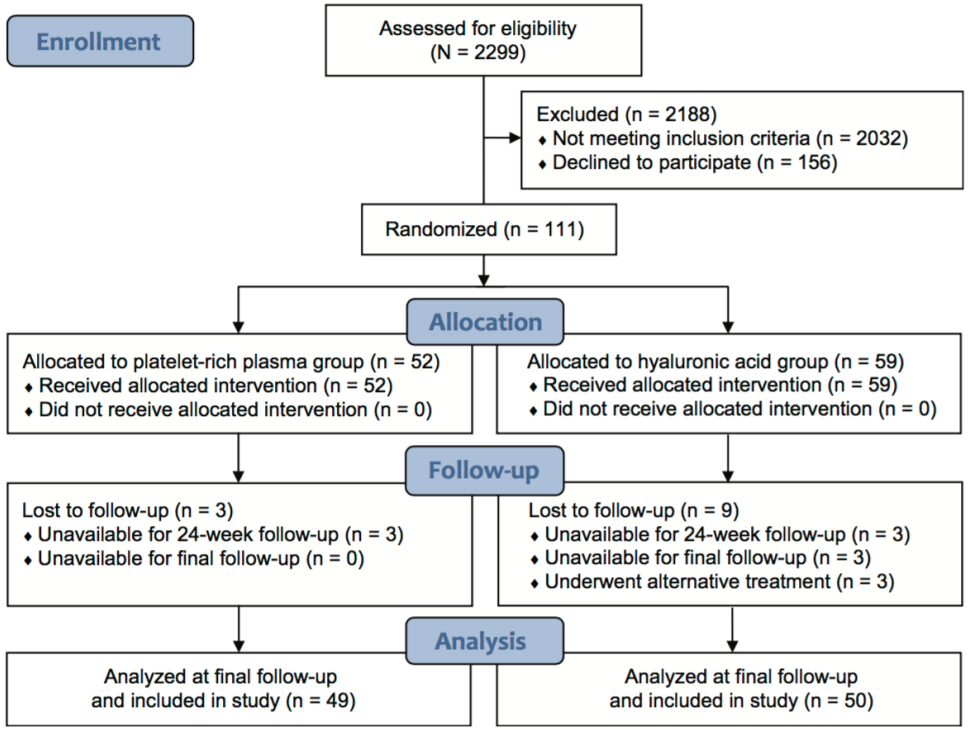


TABLE 3
WOMAC Pain Score at Study Time Points[a]

	PRP Group	HA Group
Before treatment	7.00 ± 0.53	7.52 ± 0.58
Treatment visit 2 (week 2)	6.15 ± 0.54	6.32 ± 0.55
Treatment visit 3 (week 3)	5.06 ± 0.48	5.53 ± 0.51
Follow-up		
6 weeks	4.57 ± 0.48	4.66 ± 0.47
12 weeks	3.98 ± 0.63	5.00 ± 0.60
24 weeks	4.11 ± 0.56	5.00 ± 0.50
52 weeks	3.02 ± 0.48	4.00 ± 0.60

No difference in WOMAC Pain

Hyaluronic Acid Versus Platelet-Rich Plasma

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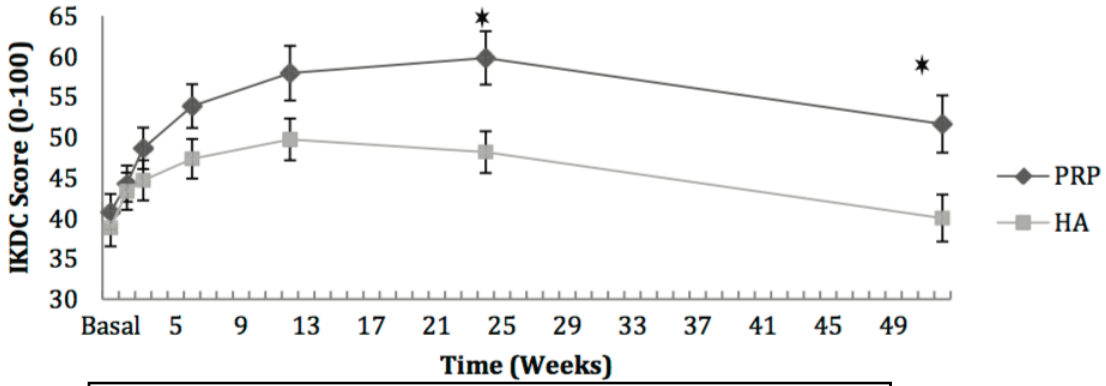
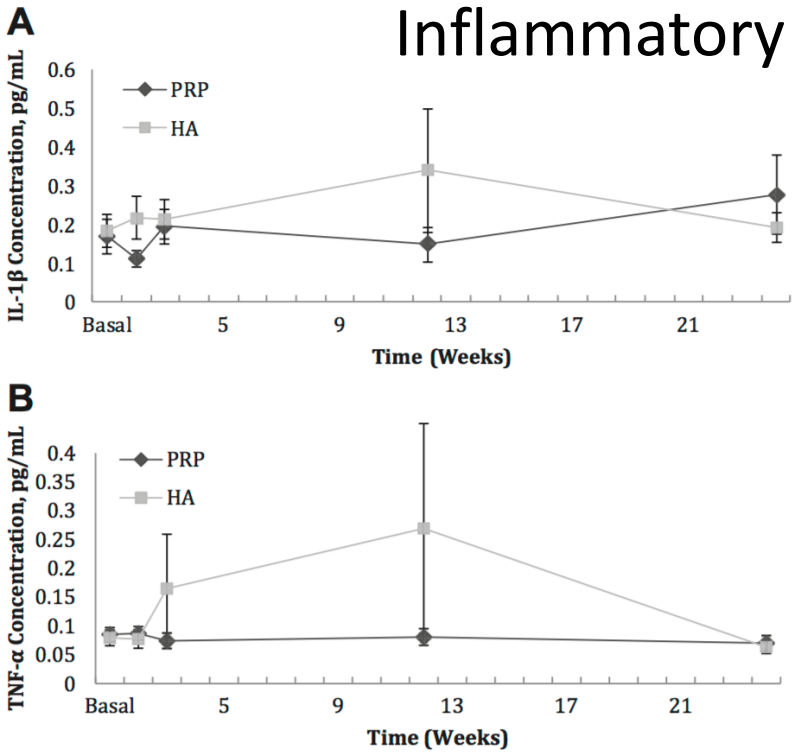
AJSM 2017



Improved IKDC Scores 6-12 Months with PRP

Inflammatory markers



Mild OA, lower BMI worked better
lowers pro-inflammatory cytokines.

Conclusion: “significant improvements were seen in other patient-reported outcome measures, with results favoring PRP over HA.”

Systematic Reviews of Level 1 and Level 2 evidence

Khoshbin et al Arthrosc 2013

Chang et al APMR 2014

Riboh et al AJSM 2015

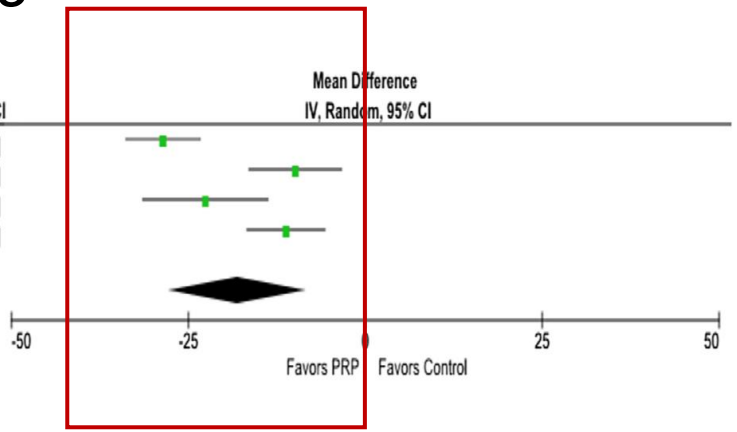
Meheux Arthros 2016

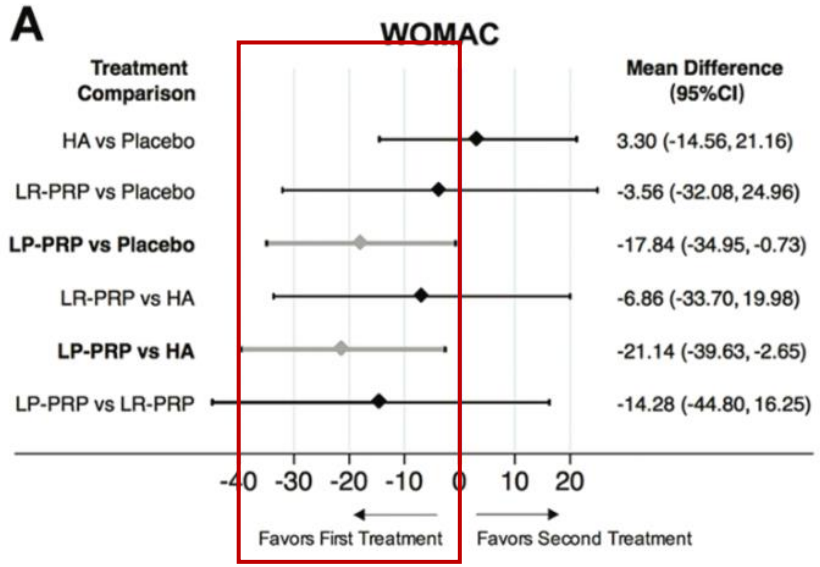
A WOMAC

Study or Subgroup	PRP Mean	PRP SD	PRP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cerza 2012	36.5	17.9	60	65.1	10.6	60	26.1%	-28.60 [-33.86, -23.34]
Li 2011	10.7	9.9	15	20.6	8.3	15	25.1%	-9.90 [-16.44, -3.36]
Patel 2013	30.5	25.9	50	53.1	17.9	46	22.9%	-22.60 [-31.45, -13.75]
Spakova 2012	18.9	14.1	60	30.1	16.6	60	25.9%	-11.20 [-16.71, -5.69]
Total (95% CI)			185			181	100.0%	-18.03 [-27.75, -8.30]

Heterogeneity: Tau² = 87.07; Chi² = 28.33, df = 3 (P < 0.00001); I² = 89%

Test for overall effect: Z = 3.63 (P = 0.0003)



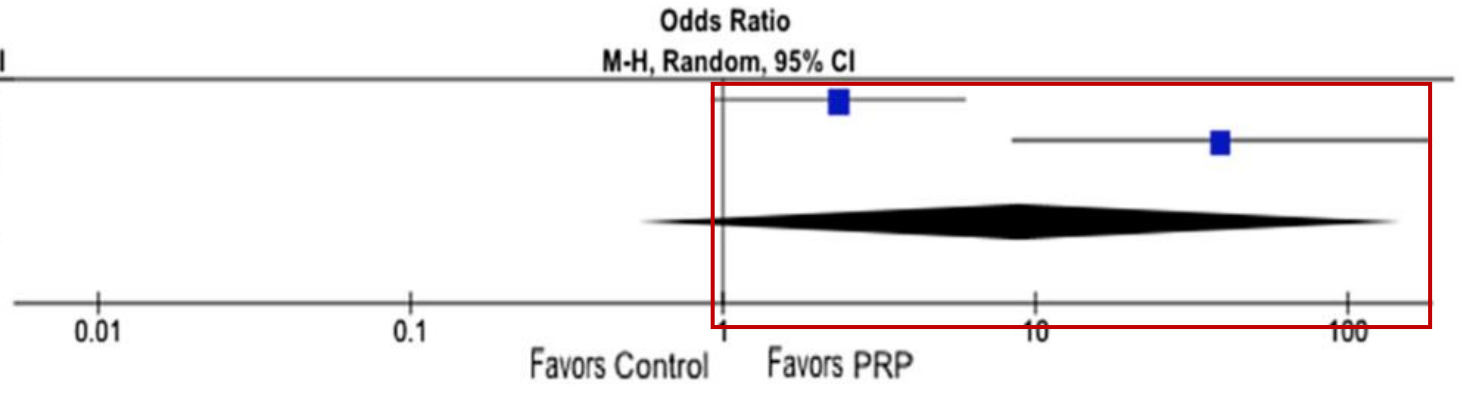


D Patient Satisfaction

Study or Subgroup	PRP Events	PRP Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Kon 2011	41	50	33	50	52.3%	2.35 [0.93, 5.94]
Patel 2013	32	50	2	46	47.7%	39.11 [8.47, 180.66]
Total (95% CI)		100		96	100.0%	8.97 [0.54, 149.25]
Total events	73		35			

Heterogeneity: Tau² = 3.71; Chi² = 9.89, df = 1 (P = 0.002); I² = 90%

Test for overall effect: Z = 1.53 (P = 0.13)



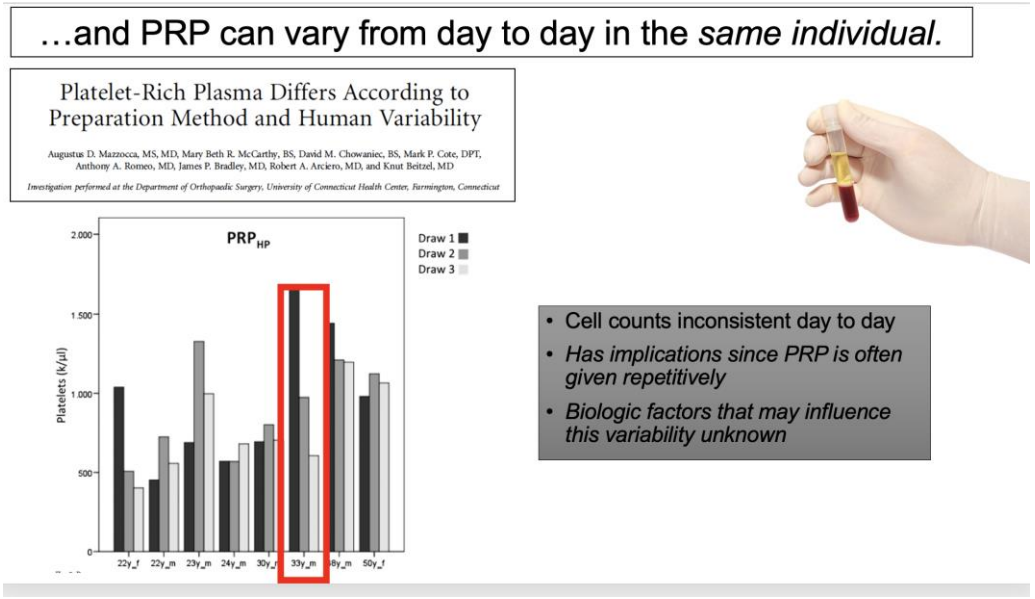
Randomized Controlled Trial > Am J Sports Med. 2021 Feb;49(2):487-496.
doi: 10.1177/0363546520986867.

Clinical Efficacy of Platelet-Rich Plasma Injection and Its Association With Growth Factors in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized Double-Blind Controlled Clinical Trial As Compared With Hyaluronic Acid

Yong-Beom Park [1], Jun-Ho Kim [2], Chul-Won Ha [3 4 5], Dong-Hyun Lee [6]

Randomized controlled trial (Level 1 evidence)

--works for all areas of the knee equally well
--more patients reached MCID with PRP vs HA
--no statistical difference in clinical outcomes

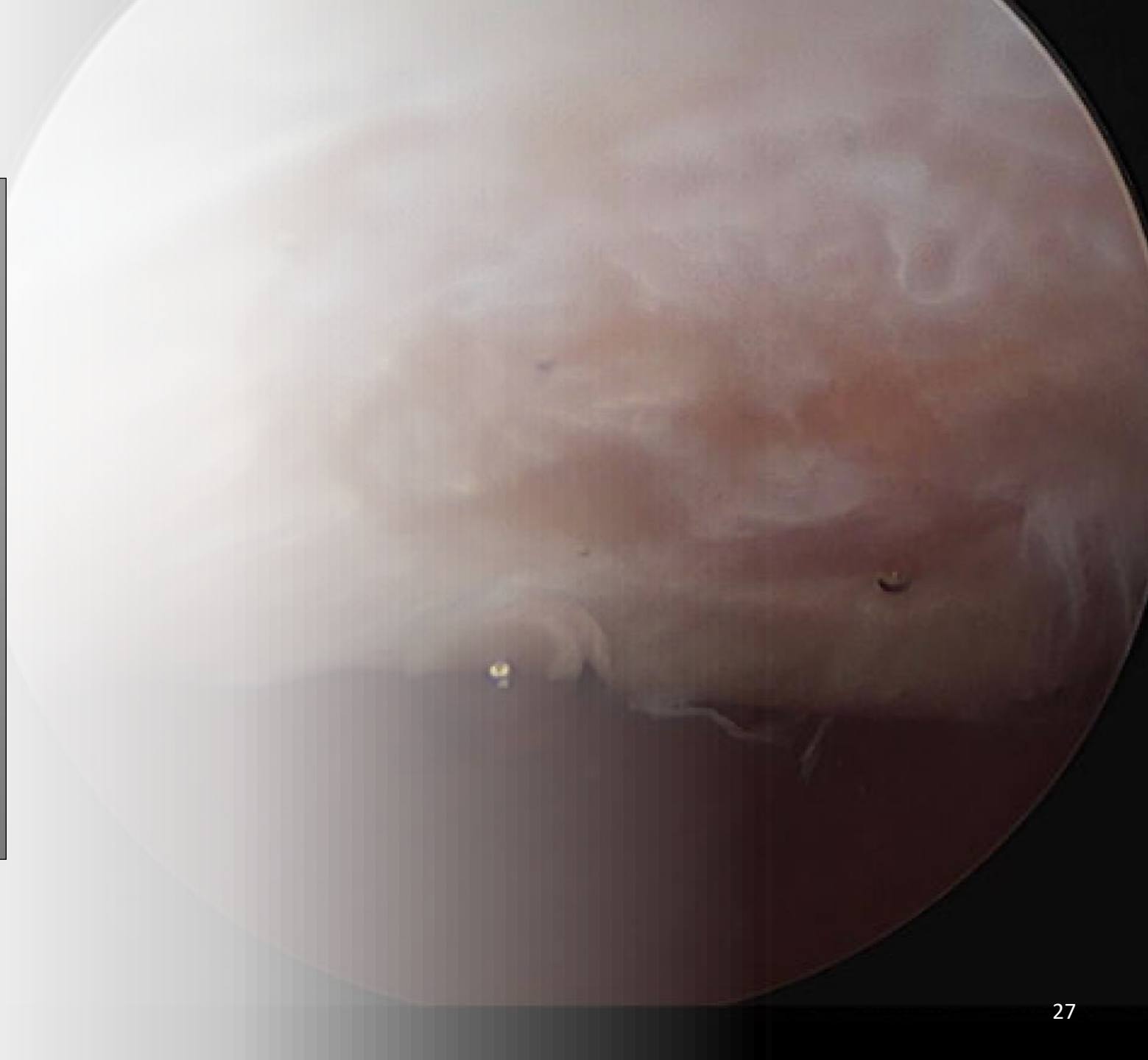


Within the PRP group, the concentrations of **platelet-derived growth factors** were high in patients with a score above the MCID for VAS at 6 months.

- **PRP and Early OA**

- Level 1, 2 evidence
- **SAFE** for patients who want to use it

- Likely beneficial with LP-PRP
- Effect size relatively small
- No long term data on natural history
- No MRI findings showing cartilage preservation Or cartilage growth



Chronic Tendonopathies

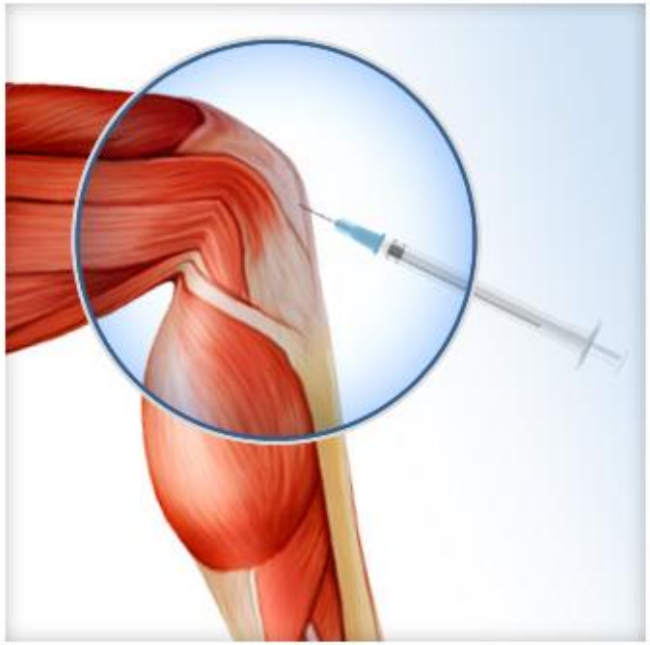
Elbow epicondylitis

Achilles tendinopathy

Jumper’s knee

Conditions that have not done well historically with surgical treatment

- Increased growth factors in necrotic, degenerative tissue areas

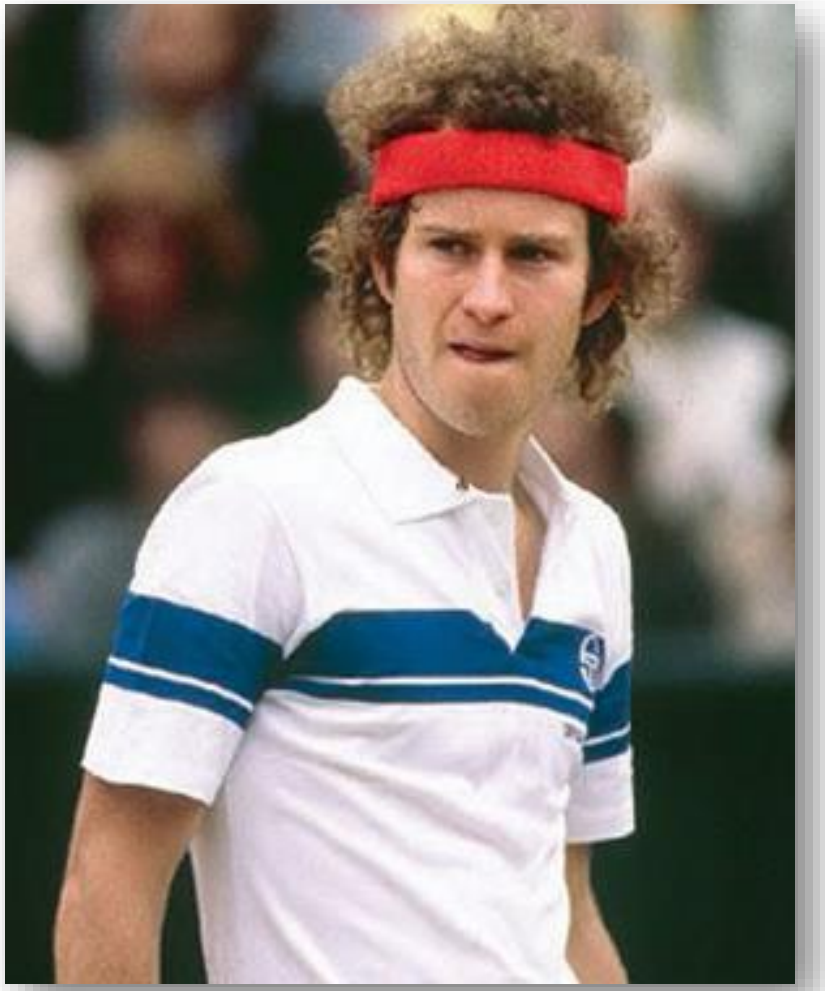


Treatment of Chronic Elbow Tendinosis With Buffered Platelet-Rich Plasma

Allan Mishra,* MD, and Terri Pavelko, PAC, PT
From the Department of Orthopedic Surgery, Menlo Medical Clinic, Stanford University Medical Center, Menlo Park, California

AJSM 2006

- Level II evidence
- 20 patients with refractory epicondylar pain
  - PRP w **WBC** single injection vs. bupivicaine
- 6 month time point, PRP group with 81% improvement in VAS scores
- 25-month f/u – PRP group with 93% reduction in pain



Efficacy of Platelet-Rich Plasma for Chronic Tennis Elbow

A Double-Blind, Prospective, Multicenter, Randomized Controlled Trial of 230 Patients

Allan K. Mishra,*† MD, Nebojsa V. Skrepnik,‡ MD, PhD, Scott G. Edwards,§ MD, Grant L. Jones,|| MD, Steven Sampson,¶ DO, Doug A. Vermillion,# MD, Matthew L. Ramsey,** MD, David C. Karli,†† MD, MBA, and Arthur C. Rettig,‡‡ MD
Investigation performed at Department of Orthopaedic Surgery, Menlo Medical Clinic, Stanford University Medical Center, Menlo Park, California

AJSM 2014

- RCT, level II, double-blinded
- 230 pt, chronic lateral epicondylar tendinopathy 3 mo in duration
  - 116 in PRP, leukocyte-enriched
  - 114 in active control
- 12-week no difference
- 24-week significant improvement in pain and reduced tenderness

Summary for Lateral Epicondylitis

Decent level 1 evidence to support PRP over steroid to improve symptoms

Use LR-PRP for lateral epicondylitis

2019

The effects of regenerative injection therapy compared to corticosteroids for the treatment of lateral Epicondylitis: a systematic review and meta-analysis

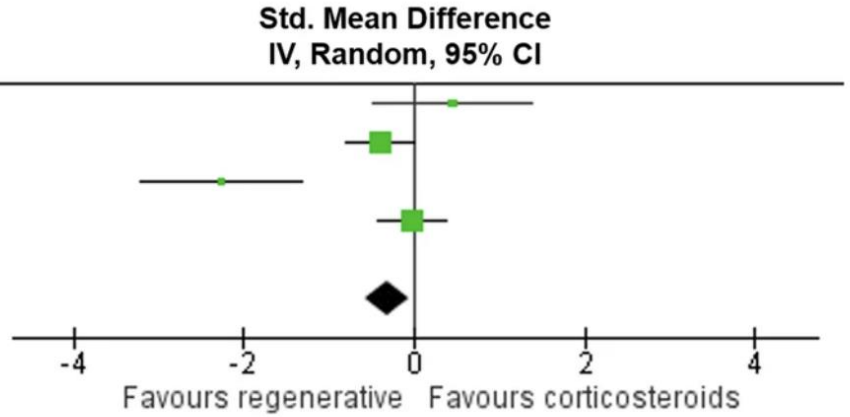
Julie Barnett ✉, Madison N. Bernacki, Jessica L. Kainer, Hannah N. Smith, Annette M. Zaharoff & Sandeep K. Subramanian

B

Six months

Study or Subgroup	Regenerative Injections Mean	SD	Total	Corticosteroids Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Wolf et al 2011	20	16.3	9	13	12.8	9	7.5%	0.45 [-0.48, 1.39]	2011
Gosens et al 2012	27.8	24.7	51	37.6	23.1	49	42.4%	-0.41 [-0.80, -0.01]	2012
Gautam et al 2015	32	4.5	15	39.6	1	15	7.5%	-2.27 [-3.21, -1.32]	2015
Lebiedzinskie et al 2015	14.2	13.4	53	14.7	22	46	42.6%	-0.03 [-0.42, 0.37]	2015
Total (95% CI)			**128**			**119**	**100.0%**	**-0.32 [-0.58, -0.06]**	

Heterogeneity: Chi² = 21.26, df = 3 (P < 0.0001); I² = 86%
Test for overall effect: Z = 2.42 (P = 0.02)

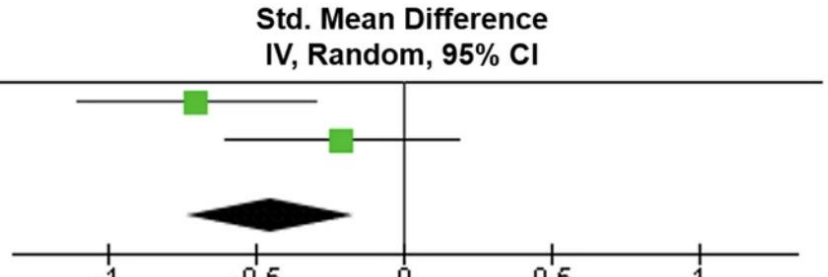


C

One year

Study or Subgroup	Regenerative Injections Mean	SD	Total	Corticosteroids Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Gosens et al 2012	20	23.5	51	36.8	24	49	49.0%	-0.70 [-1.11, -0.30]	2012
Lebiedzinskie et al 2015	9.9	17.1	53	14.4	25.2	46	51.0%	-0.21 [-0.61, 0.19]	2015
Total (95% CI)			**104**			**95**	**100.0%**	**-0.45 [-0.73, -0.17]**	

Heterogeneity: Chi² = 2.90, df = 1 (P = 0.09); I² = 66%

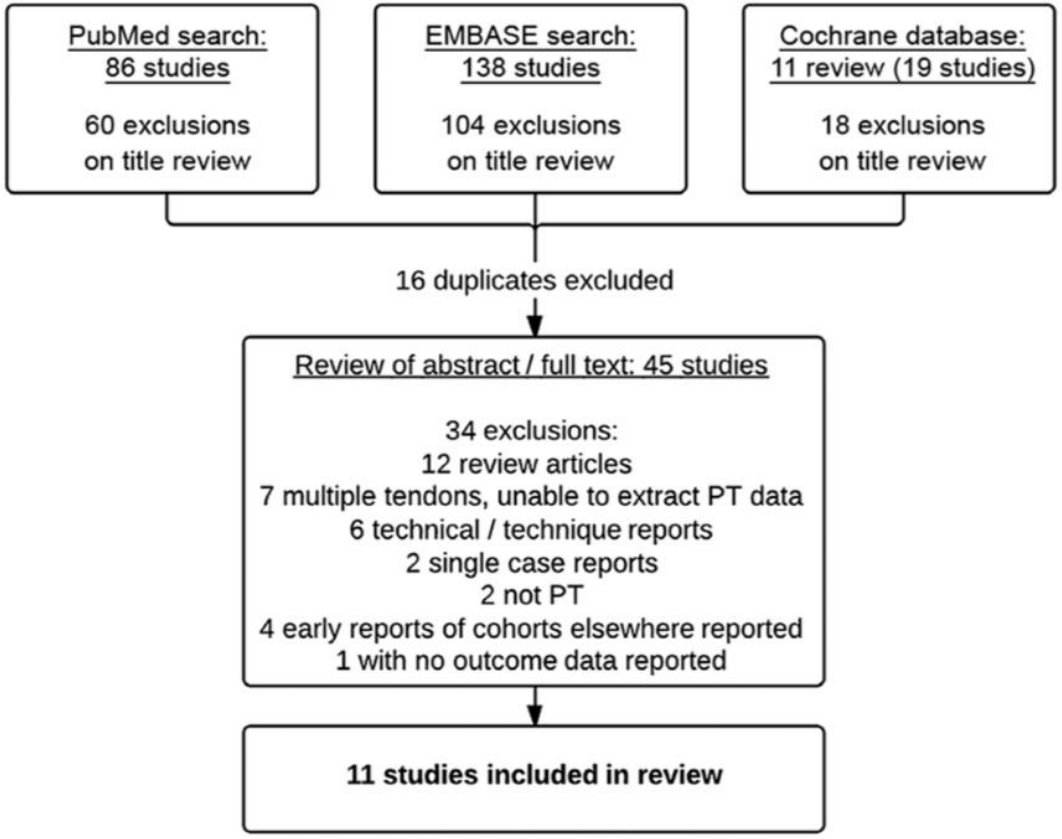


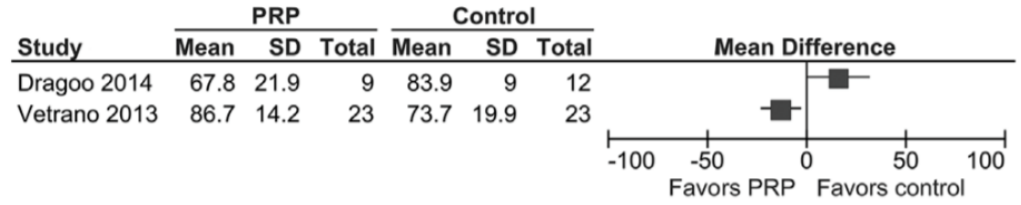
Platelet-Rich Plasma in the Treatment of Patellar Tendinopathy

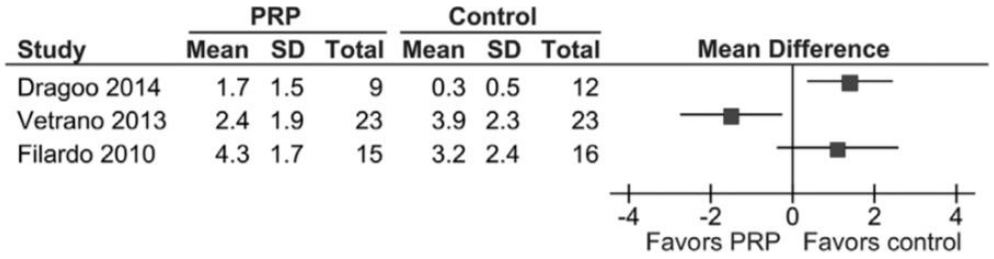
A Systematic Review

Alexander D. Liddle,* BSc, MRCS, and E. Carlos Rodríguez-Merchán,†‡ MD, PhD
Investigation performed at La Paz University Hospital, Madrid, Spain

AJSM 2015







Conclusions:
"Platelet-rich plasma is a safe and promising therapy in the treatment of recalcitrant PT. However, its superiority over other treatments such as physical therapy remains unproven."

What about PRP for tendonopathy/PTRCT?

Eur J Orthop Surg Traumatol. 2016 Aug 20. [Epub ahead of print]

Subacromial injection of autologous platelet-rich plasma versus corticosteroid for the treatment of symptomatic partial rotator cuff tears.

Shams A[1], El-Sayed M[2], Gamal O[1], Ewes W[3].

EJOST 2016

Randomized patients with partial tears to steroid vs PRP injection

Both groups got better

PRP slightly better than steroid at 12 weeks

No difference at 6 months

No difference in MRI findings at 6 months

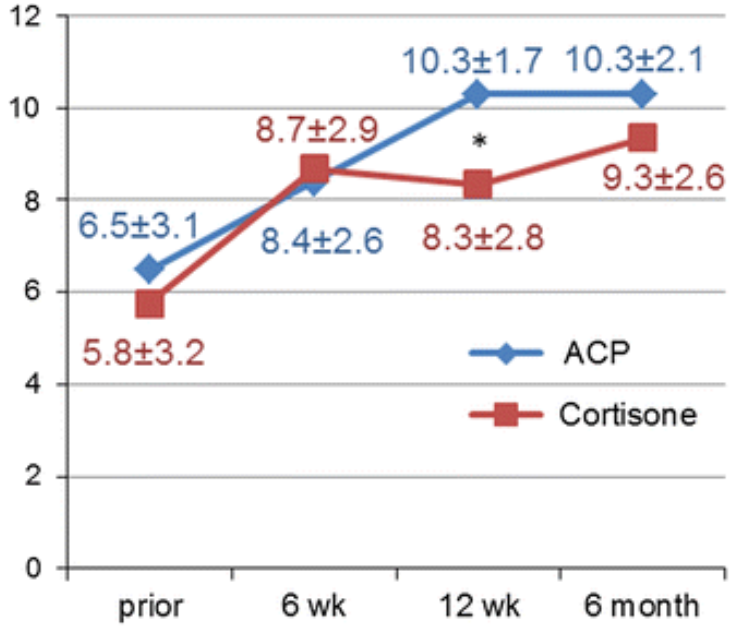
What about PRP for tendonopathy/PTRCT?

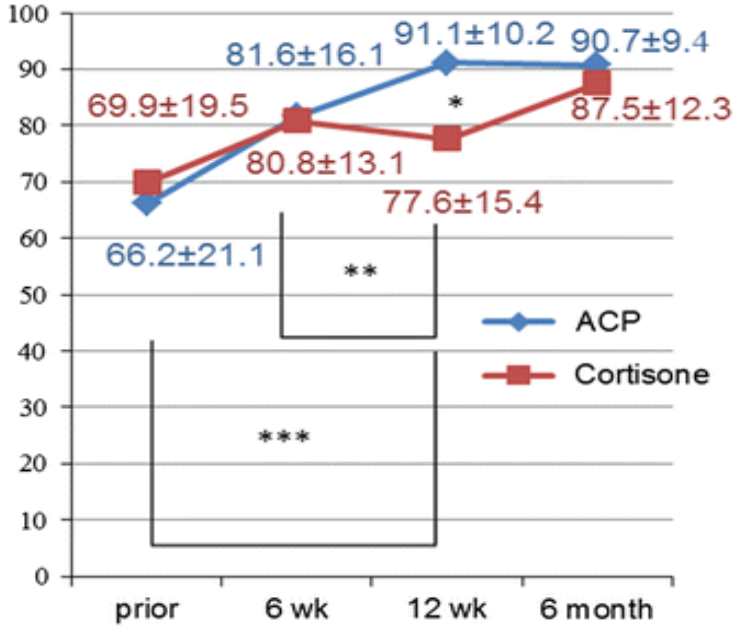
Knee Surg Sports Traumatol Arthrosc. 2015 May 28. [Epub ahead of print]

The effect of subacromial injections of autologous conditioned plasma versus cortisone for the treatment of symptomatic partial rotator cuff tears.

von Wehren L[1], Blanke F, Todorov A, Heisterbach P, Sailer J, Majewski M.

KSSTA 2015

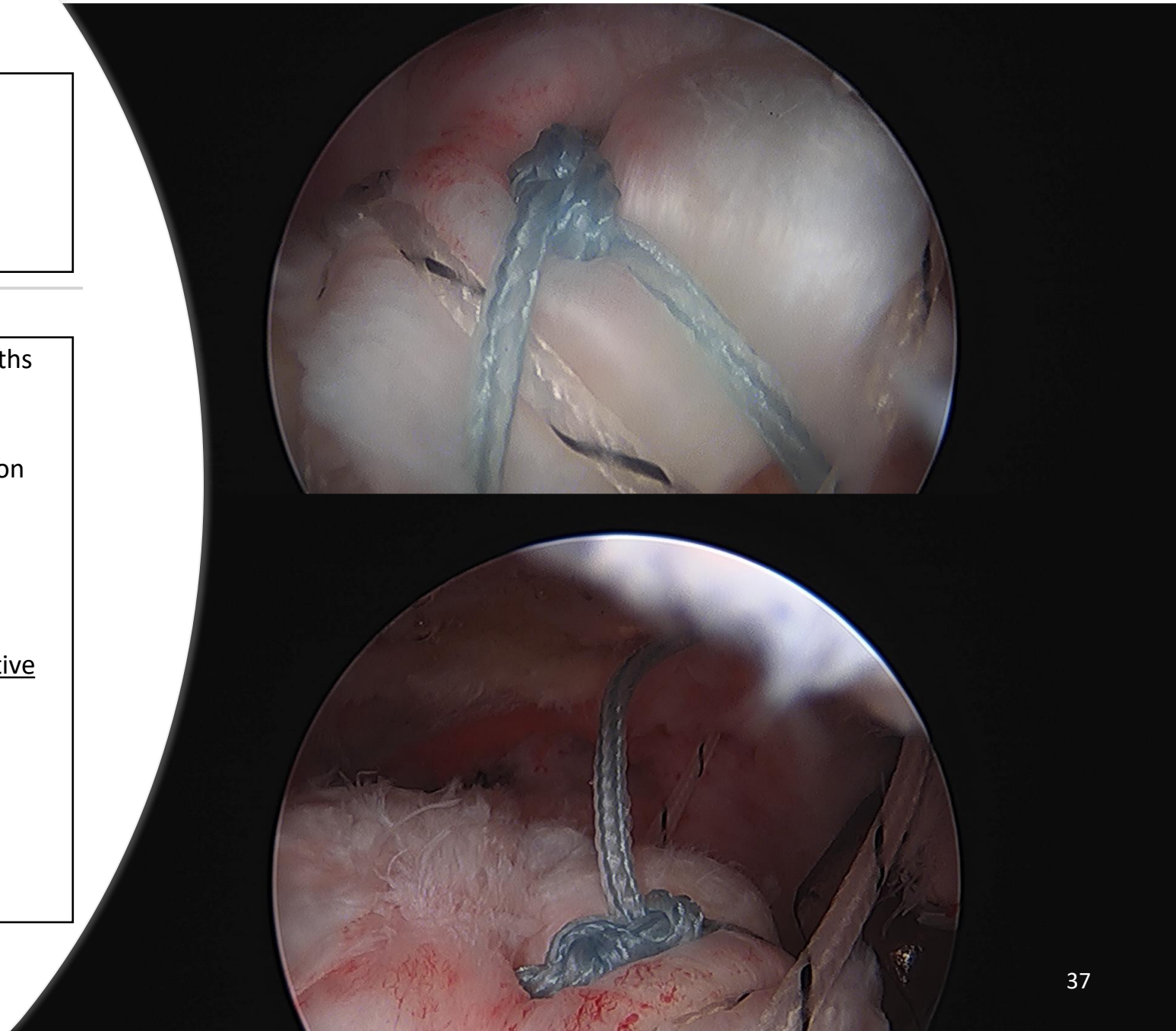




Slight improvement with PRP at 3 months, no difference at 6 months

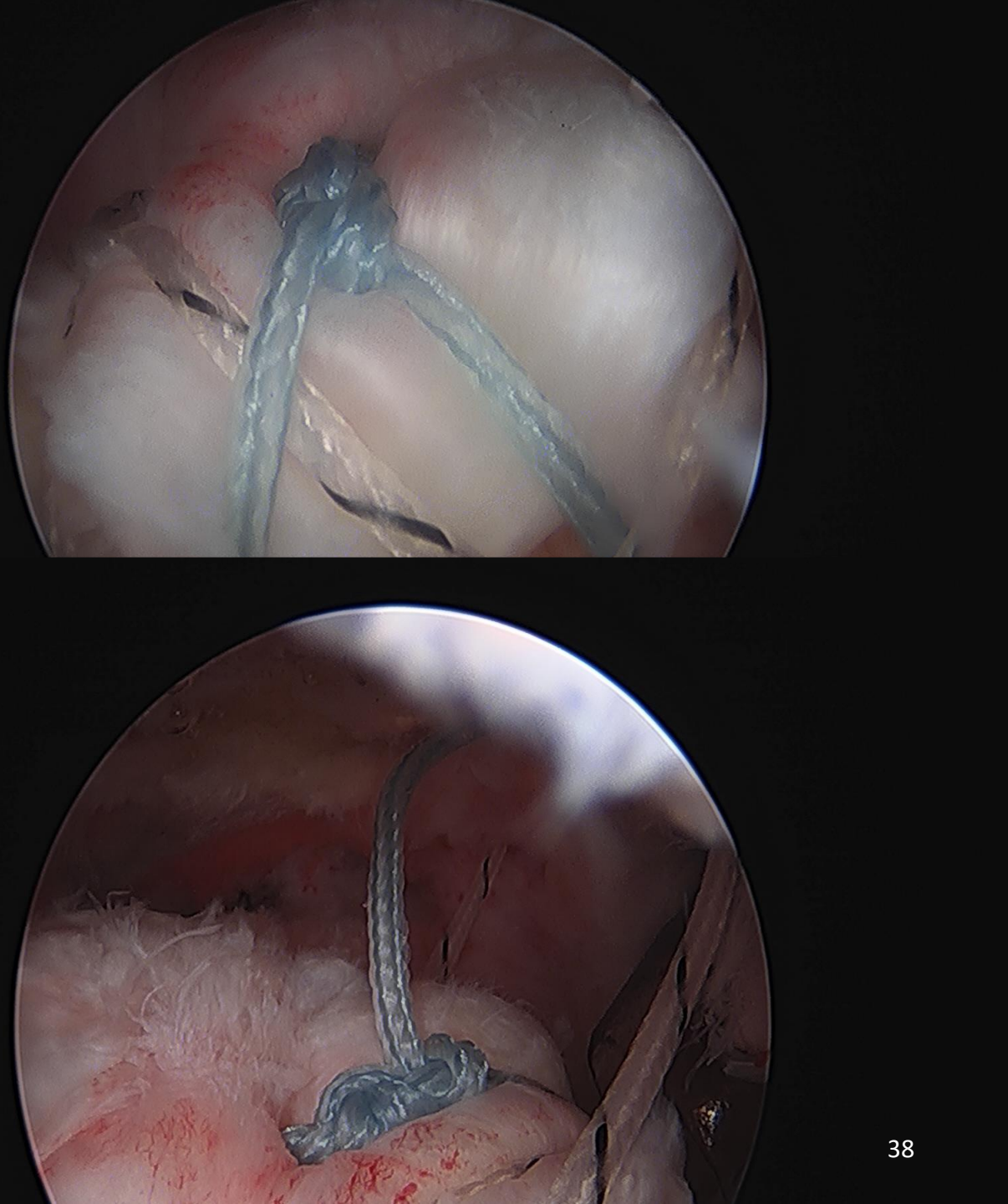
Rotator Cuff Repair Studies
PRP doesn't work!

- No difference in UCLA scores outcomes at 6, 12, 24 months
  - ***Randelli et al JSES 2011***
- No significant difference in Constant and tendon scores on MRI
  - ***Castricini et al AJSM 2011***
  - ***Wang et al AJSM 2015***
- No difference in clinical scores at 1-yr f/u, possible negative effect on healing
  - ***Jo et al AJSM 2011***
  - ***Rodeo et al AJSM 2012***
  - ***Weber et al AJSM 2015***



Rotator Cuff Repair Studies
PRP might work?

- Early pain reduction, no difference in healing
  - ***D'Ambroisi MSK Surg 2016***
  - ***Holtby AJSM 2016***
- Improved healing in large tears (SR only)
  - ***Pandey JSES 2016***
  - ***Jo et al AJSM 2015***
    - *(3% PRP vs 20% Control)*

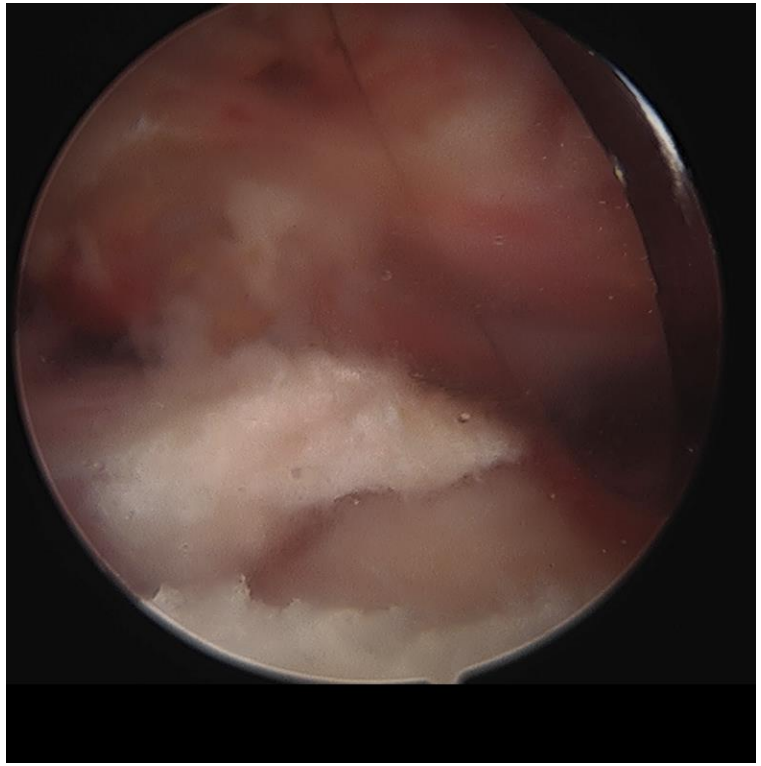


Am J Sports Med. 2018 Nov;46(13):3134-3141. doi: 10.1177/0363546518795895. Epub 2018 Sep 20.

Clinical and Structural Evaluations of Rotator Cuff Repair With and Without Added Platelet-Rich Plasma at 5-Year Follow-up: A Prospective Randomized Study.

Malavolta EA[1], Gracitelli MEC[1], Assunção JH[1], Ferreira Neto AA[1], Bordalo-Rodrigues M[1], de Camargo OP[1].

- Prospective RCT of 54 patients at 5 years after RC repair of small to medium tears
  - No difference in clinical outcomes
  - No difference in retear rates
  - **“PRP did not enhance healing rates or clinical outcomes at 5 years”**



Platelet-Rich Product Supplementation in Rotator Cuff Repair Reduces Retear Rates and Improves Clinical Outcomes: A Meta-Analysis of Randomized Controlled Trials

Arthroscopy 2021

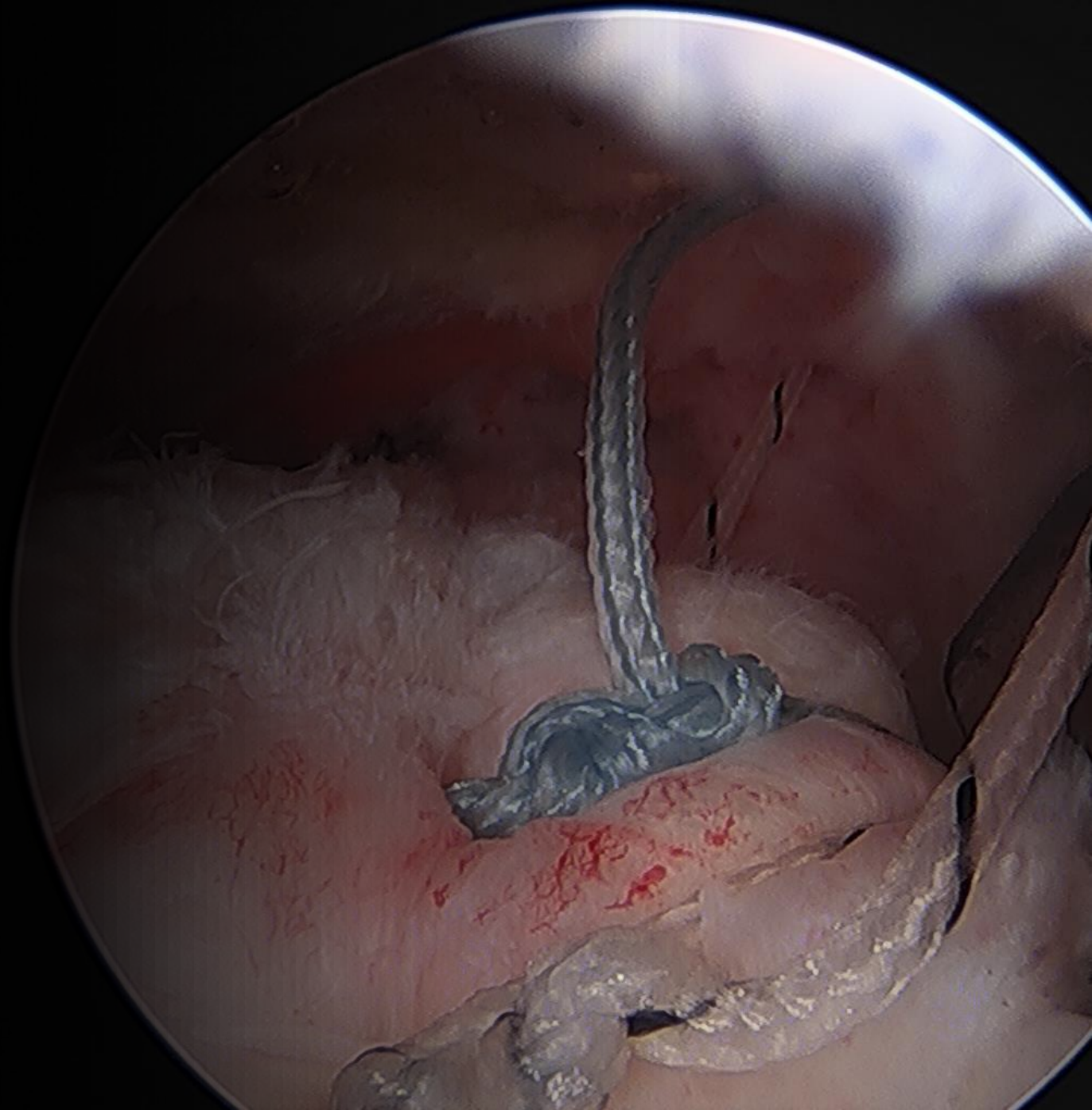
James Ryan [1], Casey Imbergamo [2], Suleiman Sudah [3], Greg Kirchner [4], Patricia Greenberg [2], James Monica [2], Charles Gatt [2]

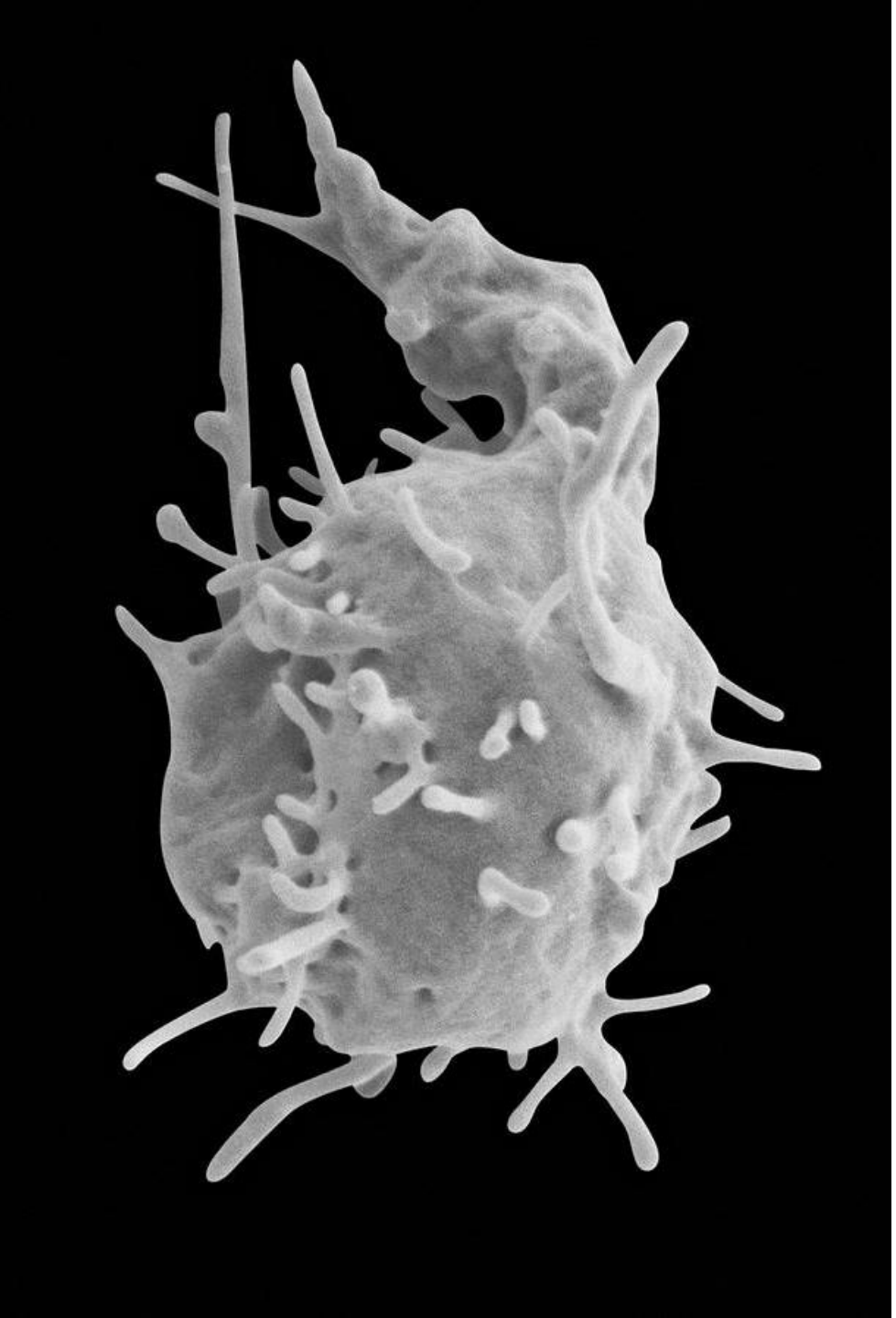
Compared different types of PRP---only ‘pure’ PRP seemed to make a difference

Retear rates were lower--19% vs 25%
Constant score better—did not meet MCID
ASES, UCLA score no different

Summary for rotator cuff

- Not beneficial for partial tears
- May add some benefit to decrease retear rates
- Other options (scaffolds, augments) may be better





What I tell patients about PRP

- PRP is overall **SAFE**
- **Probably will make some conditions better**
- Not all formulations are the same
  - Daily concentrations of platelets and growth factors are actually different
- Seems to be effective for: Early knee OA, tennis elbow.
- Not very effective for: other tendonopathies, spine
- Clinical effects are going to be **variable**—and that's why the studies are so all over the place!

Stem cell treatments

Biologics are symptom-modifying but not structure-modifying

- Currently available “biologics” are generally believed to function by producing anti-inflammatory and immunomodulatory factors
  - Autologous blood products: PRP, autologous conditioned serum, autologous protein solution
  - Cell therapy formulations: Bone marrow aspirate, adipose-derived stromal vascular fraction, umbilical cord blood cells, amniotic tissue
- These anti-inflammatory and immune-modulating factors can lead to pain relief
- However, although numerous anabolic cytokines and growth factors are delivered by these products, there is currently very little data to suggest true tissue regeneration

I. INTRODUCTION

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

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Guidance for Industry and Food and Drug Administration Staff

Definition of Stem Cells

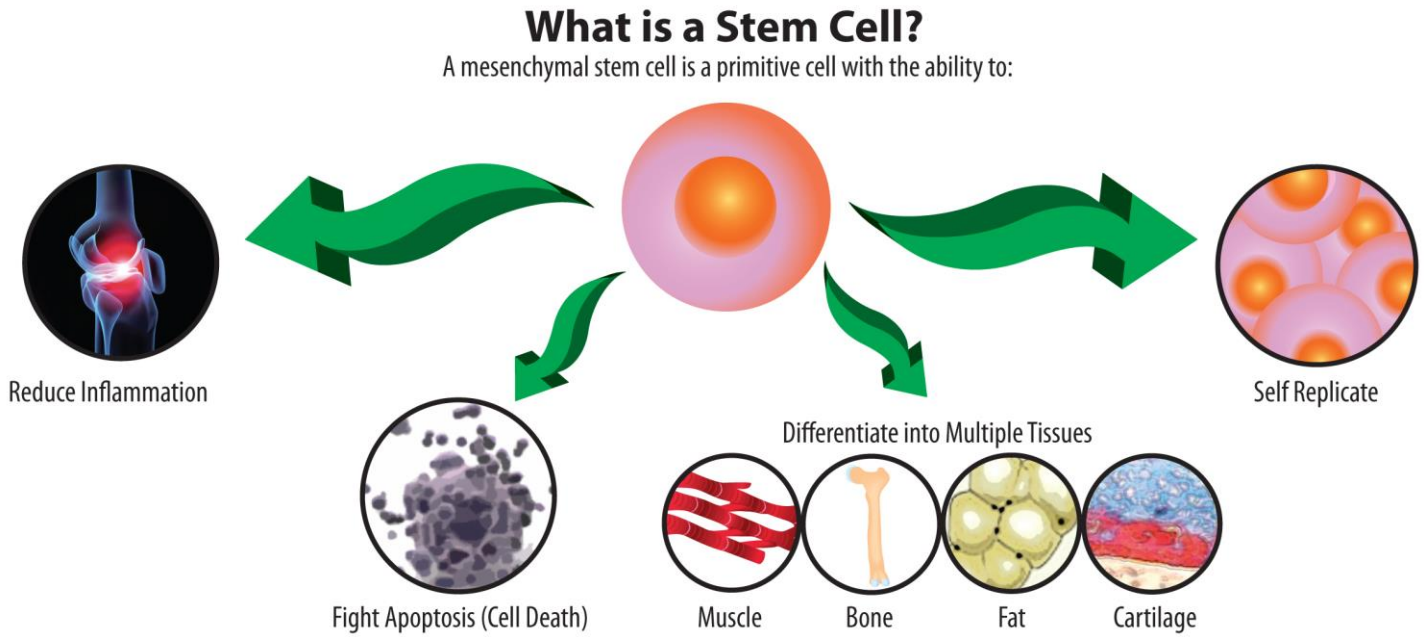
3 Key Characteristics

- Unspecialized cells
- Capable of self renewal
- Induced into specialized tissue with the right signals

Defined by their cell surface markers

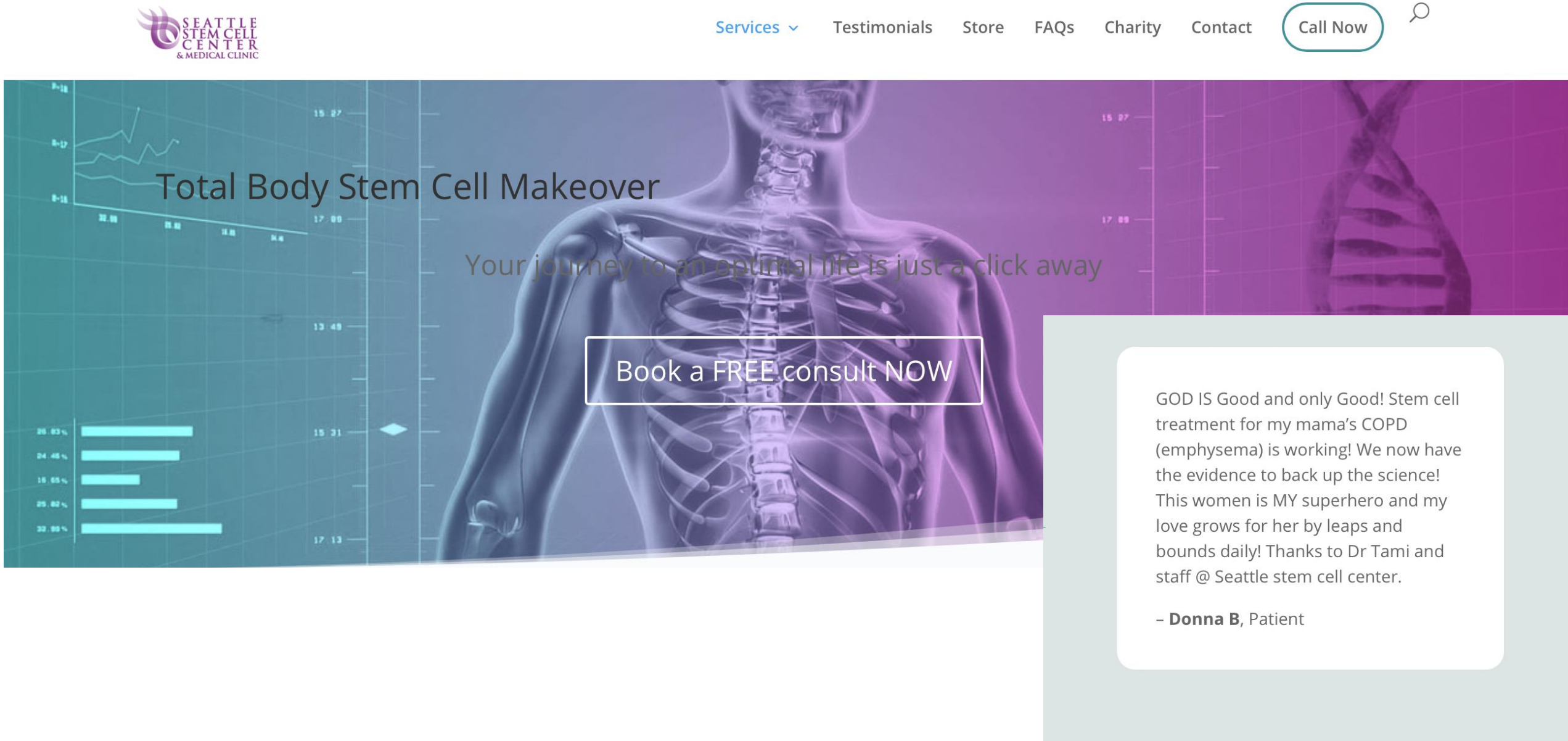
- MSCs CD117+,CD34-
- ESCs CD134, CD31-

Stem Cells



- **Adult** and Embryonic Stem Cells
  - **Mesenchymal**, hematopoietic, juvenile
    - Stromal Vascular Fraction (Fat)
  - Induced pluripotent stem cells (iPSC)
  - Amniotic Membrane

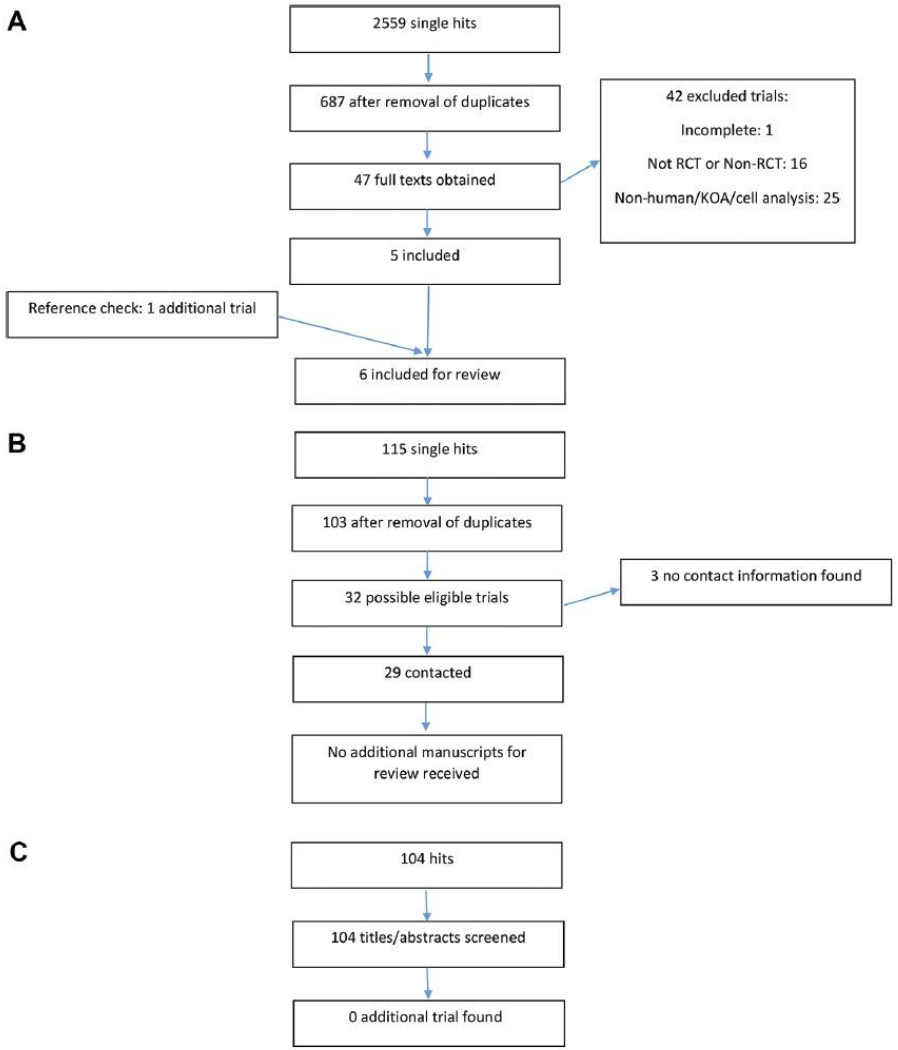
How do Stem Cells Work? (does it matter?)



Br J Sports Med. 2017 Mar 3. pii: bjsports-2016-096793. doi: 10.1136/bjsports-2016-096793. [Epub ahead of print]

Stem cell injections in knee osteoarthritis: a systematic review of the literature.

Pas HI[1,2,3], Winters M[4], Haisma HJ[5], Koenis MJ[6], Tol JL[7,3,8], Moen MH[7,9,10].



"There is level-3 or level-4 evidence for the use of stem cell injection of different types in the treatment of KOA when evaluating PROMs, pain and radiographic, arthroscopic and histological outcomes. It should be noted that all treatments **were additional to surgery, HA or PRP injections.** All studies were found to be at high risk of bias. Therefore, we do not recommend to use stem cell therapy for patients with KOA"

Concentrated Bone Marrow Aspirate for the Treatment of Chondral Injuries and Osteoarthritis of the Knee

A Systematic Review of Outcomes

Jorge Chahla,* MD, Chase S. Dean,* MD, Gilbert Moatshe,*† MD, Cecilia Pascual-Garrido,‡ MD, Raphael Serra Cruz,*§ MD, and Robert F. LaPrade,*||¶ MD, PhD

Investigation performed at Steadman Philippon Research Institute, Vail, Colorado, USA

Orthop J Sports Med. 2016 Jan 13;4(1):2325967115625481.

* varying degrees of beneficial results with the use of BMAC

TABLE 3
Knee Osteoarthritis Studies[a]

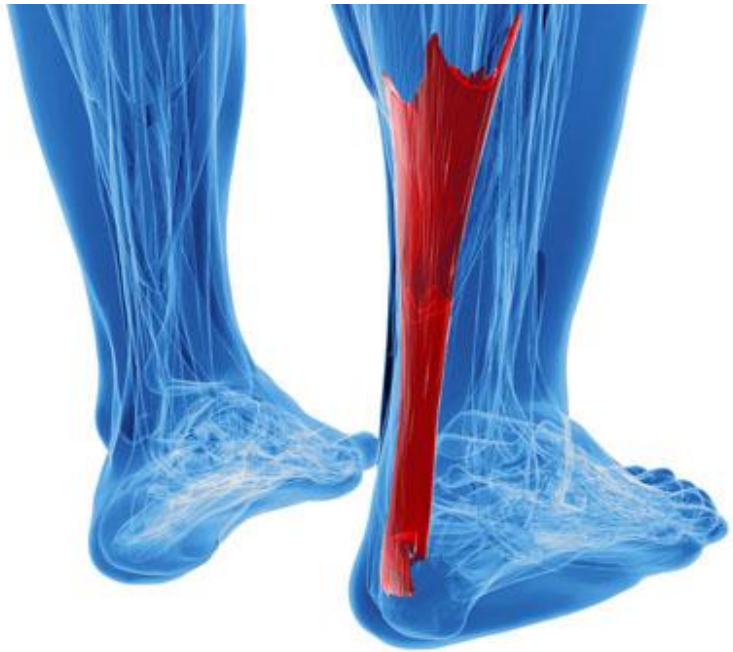
Study	Study Type (N)	Age, y, Mean (Range)	Follow-up, mo (Range)	Pathology	Treatment	Additional Factors	Results	Conclusion	Complications

Conclusion: “there still remains a paucity of high-quality studies……..Studies reviewed reported varying degrees of beneficial results with the use of BMAC with and without an additional procedure for the treatment of chondral defects and early OA. Most articles present the use of BMAC as a safe procedure and report good results”

Br J Sports Med. 2017 Jan 11. pii: bjsports-2016-096794. doi: 10.1136/bjsports-2016-096794. [Epub ahead of print]

No evidence for the use of stem cell therapy for tendon disorders: a systematic review.

Pas HI[1,2], Moen MH[1,3,4], Haisma HJ[5], Winters M[6].



What are the findings?

- The current level of evidence for stem cell use in tendon disorders is extremely poor.
- Only case reports or poorly designed trials are available.
- The results from the identified trials are at high risk of bias.

How might it impact on clinical practice in the future?

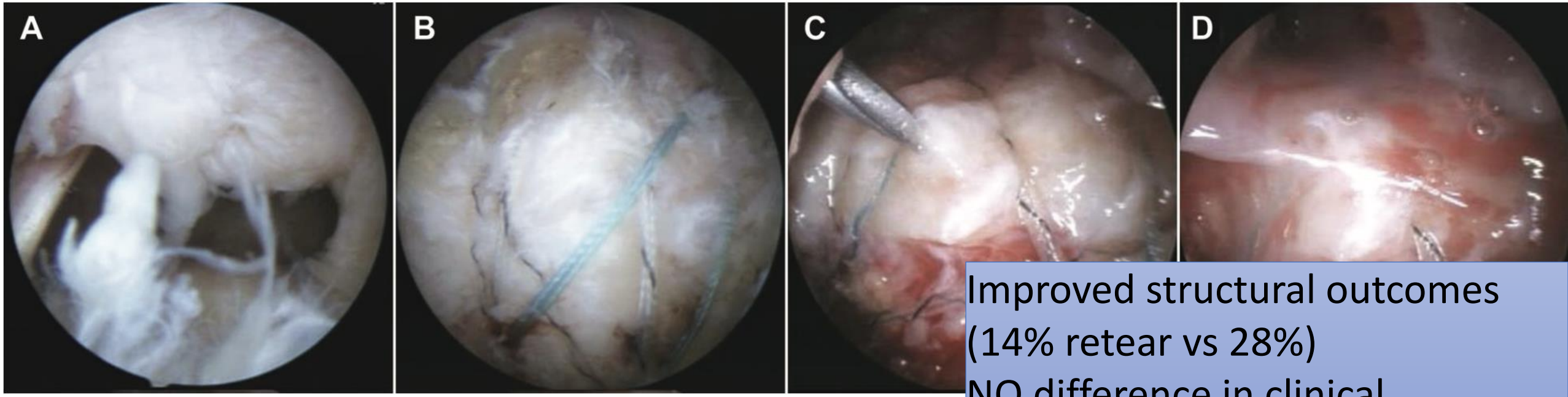
- The use of stem cell therapy for tendon disorders in clinical practice is not suitable outside of an appropriate ethics approved clinical trial.
- Patients seeking stem cell treatment for their tendon disorders can now be made aware of the lack of evidence and potential dangers.
- In cases where stem cells are used, safety must be monitored and reported by the investigator.

Evidence that Stem Cell Therapy Works for Musculoskeletal Conditions

Am J Sports Med. 2017 Apr 1:363546517702863. doi: 10.1177/0363546517702863. [Epub ahead of print]

Does an Injection of Adipose-Derived Mesenchymal Stem Cells Loaded in Fibrin Glue Influence Rotator Cuff Repair Outcomes? A Clinical and Magnetic Resonance Imaging Study.

Kim YS[1], Sung CH[1], Chung SH[1], Kwak SJ[2], Koh YG[1].

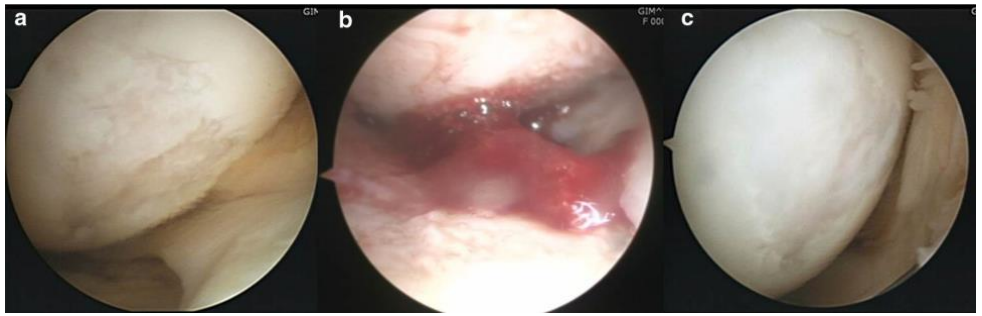


Improved structural outcomes (14% retear vs 28%)
NO difference in clinical outcomes

Culture-expanded cells CAN lead to neo-tissue formation

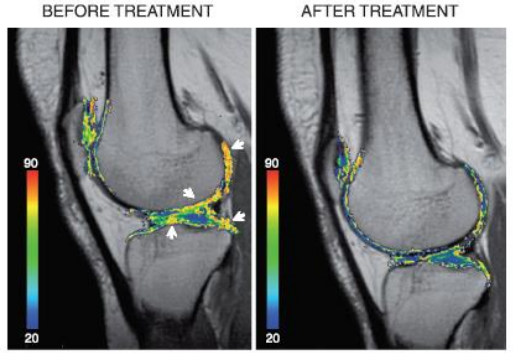
Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee OA
Koh et al, KSSTA 2015

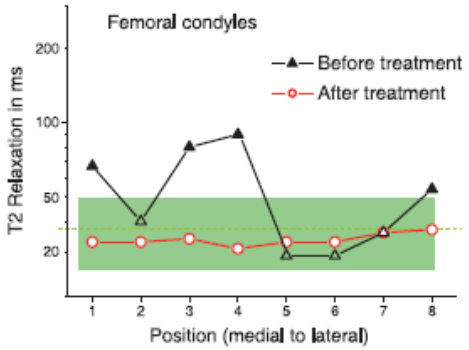
- Lipoaspiration 1 day pre-op → centrifugation in lab
- Mean 4.1 × 10^6 adipose stromal vascular fraction cells + arthroscopic lavage
- N=30 elderly patients (≥65 years) with knee OA
- Majority had significant improvement in all clinical outcomes at final F/U
- Improved or maintained cartilage status at 2 years post-op on second-look arthroscopy in 14/16 patients



Treatment of Knee OA With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial
Vega et al, Transplantation 2015

- Allogeneic culture-expanded bone marrow MSCs by intra-articular injection of 40 × 10^6 cells N=15
- Control group: hyaluronic acid injection N=15
- The MSC-treated patients displayed significant improvement in functional indices versus controls treated with hyaluronic acid
- MRI T2 relaxation measurements showed

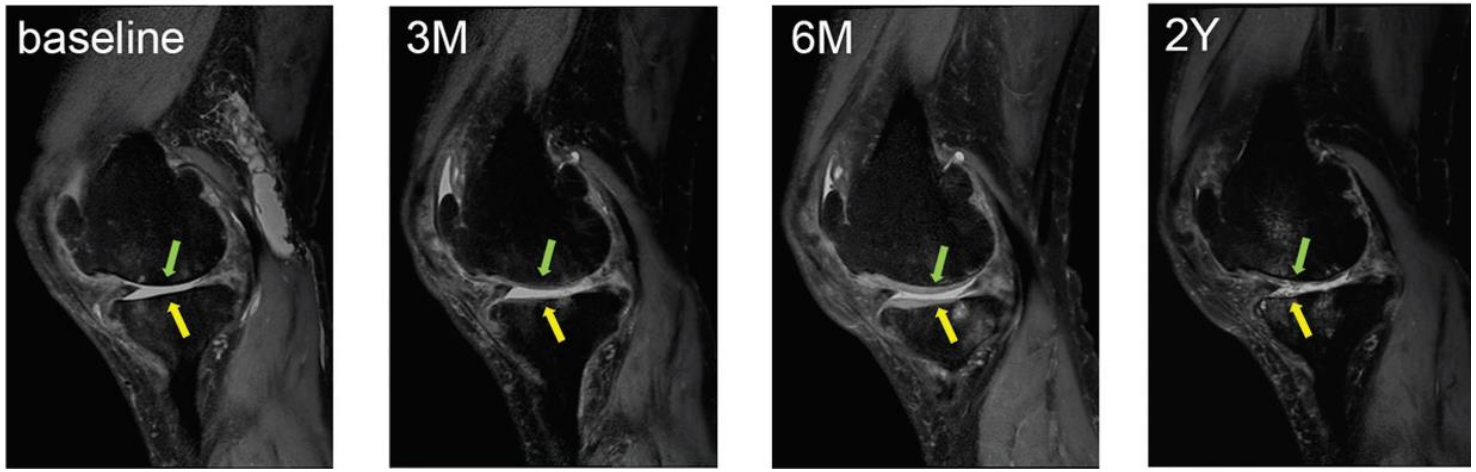




However, function and durability of regenerative tissue unknown

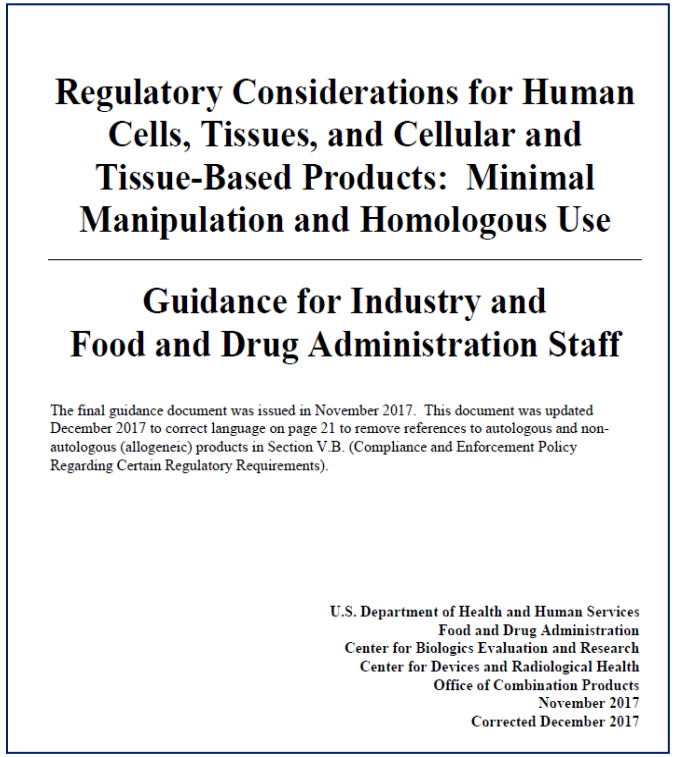
Intra-articular Injection of Mesenchymal Stem Cells for the Treatment of OA of the Knee: A 2-Year Follow-up Study.
Jo et al, American J. Sports Medicine 2017

- Injection of autologous adipose tissue-derived MSCs for knee OA N=18 with knee OA (mean age, 61.8 yr)
- Low-, medium-, and high-dose groups (1.0×10^7, 5.0×10^7, and 1.0×10^8 MSCs)
- MSCs improved knee function (WOMAC, Knee Society clinical rating system, VAS, and KOOS)
- Better results in the high-dose group at 2 years
- Some cartilage regeneration seen in high dose group, but this tissue then gradually disappeared
- **Conclusion**: Potential concerns about the durability of clinical and structural outcomes



The current regulatory environment in the U.S. prohibits cell sorting and culture expansion of cell therapy formulations

- It is important to distinguish cell populations freshly harvested from native tissues from culture-expanded cell populations
- We cannot perform ex-vivo “manipulation” of cell formulations (cell sorting, culture expansion, etc.)
- The number of true “stem cells” by cellular, molecular, or functional criteria in currently used formulations is vanishingly small
- Culture-expanded populations are highly selected and fundamentally different from the mixed starting population of progenitor cells that contribute to their generation
- The heterogeneous cell populations currently used are poorly-characterized
- The identity and biological activity of these cells are largely unknown
- We need sentinel markers of cell purity, potency, and biological activity
- → All of this suggests that tissue regeneration to delay arthroplasty would be unlikely and unpredictable



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

The final guidance document was issued in November 2017. This document was updated December 2017 to correct language on page 21 to remove references to autologous and non-autologous (allogeneic) products in Section V.B. (Compliance and Enforcement Policy Regarding Certain Regulatory Requirements).

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
Office of Combination Products
November 2017
Corrected December 2017

FDA U.S. FOOD & DRUG ADMINISTRATION

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News & Events

Home > News & Events > Newsroom > Press Announcements

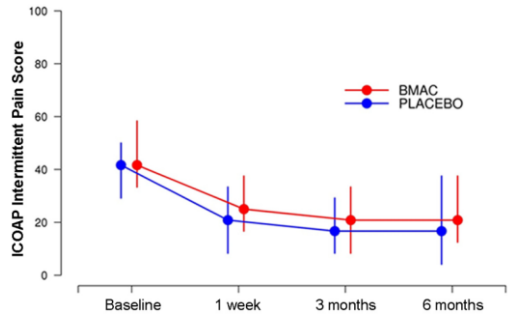
FDA News Release

FDA announces comprehensive regenerative medicine policy framework

Non-manipulated cell formulations used in the U.S. do not lead to tissue regeneration

A Prospective, Single-Blind, Placebo-Controlled Trial of Bone Marrow Aspirate Concentrate for Knee OA
Shapiro et al, American J. Sports Medicine 2017

- Single-blind, randomized placebo-controlled trial
- 25 patients with bilateral knee OA randomized: BMAC in one knee and saline placebo in other
- Cells NOT culture-expanded
- OARSI and VAS pain scores improved in both knees
- No significant difference between treated knees
- Pain relief BMAC = saline-treated arthritic knees



Quantitative T2 MRI Mapping and 12-Month Follow-up in a Randomized, Blinded, Placebo Controlled Trial of Bone Marrow Aspiration and Concentration for Osteoarthritis of the Knees
Shapiro et al, Cartilage 2019

- T2 MRI cartilage mapping at 6-month
- T2 quantitative MRI mapping showed no significant changes post-treatment
- MRI cartilage sequences failed to show regenerative benefit with single BMAC injection
- Mechanisms of action that led to pain relief not due to cartilage "regeneration"

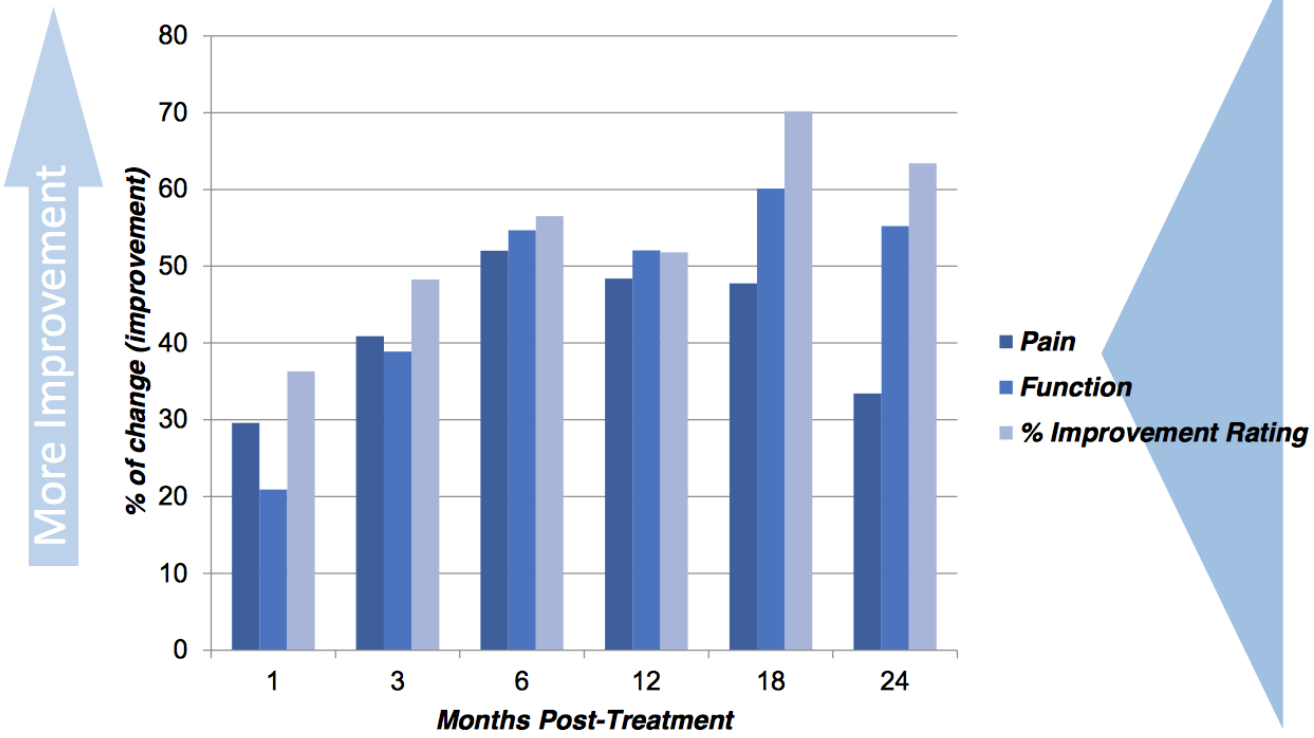
Shoulder Arthritis and Rotator Cuff Tears

N=199 Patients

Collected from 14 Clinics

2014 Registry Data

Caution-This is registry data collected as patients are treated, which is not the same as a randomized controlled trial typically used for FDA approval. In addition, later time points in this graph have more patients who did not answer questionnaires.



What's important?

This graph shows pain scores, function as measured by the DASH questionnaire, and the % improvement rating as determined by the patient at various points after the procedure. All of these are reported in terms of percentage improvement to make them easier to interpret. The outcome information shows robust improvement in both pain and function as well as high marks reported by patients when asked to rate their percentage improvement from 0-100% (% Improvement Rating). The patients represented here are a mix of rotator cuff tear only patients and patients who also had shoulder arthritis.

Details?

Mean age is 56.9 years old. BMI is 26.5. There were 56 women and 143 men. N is 199 at pre-treatment, 73 at 1 month, 83 at 3 months, 59 at 6 months, 21 at 12 months, 22 at 18 months, 15 at 24 months.

Regenexx®

Same Day Stem Cell Procedure

This procedure involves taking bone marrow stem cells from the back of the hip and re-injecting them under precise imaging guidance into the hip joint and associated structures like labrum.

Amnion and Umbilical Cord–Derived Products in Sports Medicine: From Basic Science to Clinical Application

Lisa A. Fortier, DVM, PhD*, Marta Cercone, DVM, PhD, Laura E. Keller, BS, more... Show all authors

First Published April 30, 2021 | Research Article | Find in PubMed | Check for updates
https://doi.org/10.1177/03635465211010466

Article information

Altmetric 3

AJSM July 2021

Obtained cord blood product from company and assessed for:

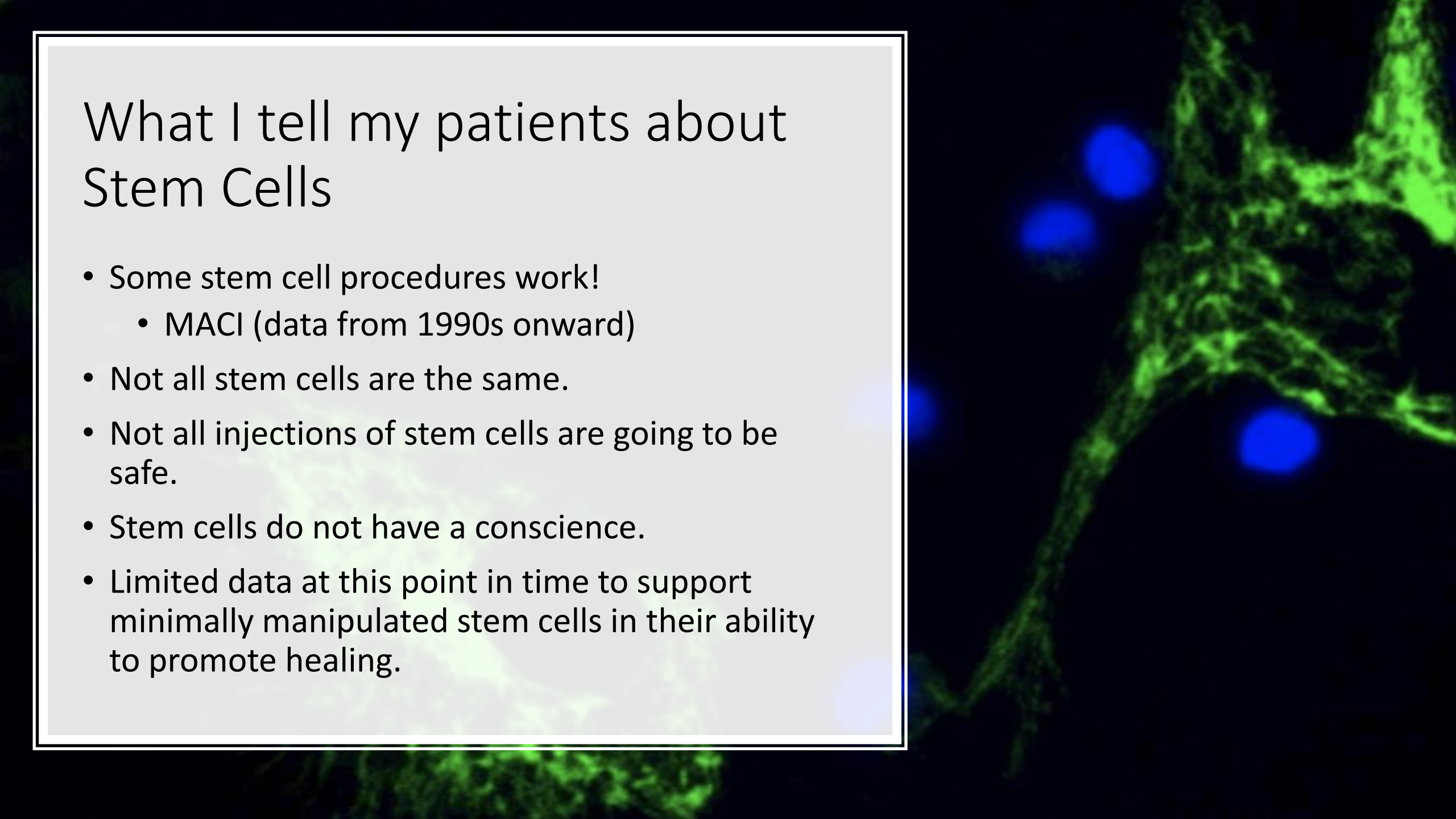
Cell viability
Cell type
Protein expression

$5500-7500

*"Cell viability in the cord blood product was less than reported by the manufacturer, the cells were primarily leukocytes, **no stem cells were present**, and the concentration of IL-1ra was falsely increased due to nonspecific antibody binding in the sample."*

What I tell my patients about Stem Cells

- Some stem cell procedures work!
  - MACI (data from 1990s onward)
- Not all stem cells are the same.
- Not all injections of stem cells are going to be safe.
- Stem cells do not have a conscience.
- Limited data at this point in time to support minimally manipulated stem cells in their ability to promote healing.



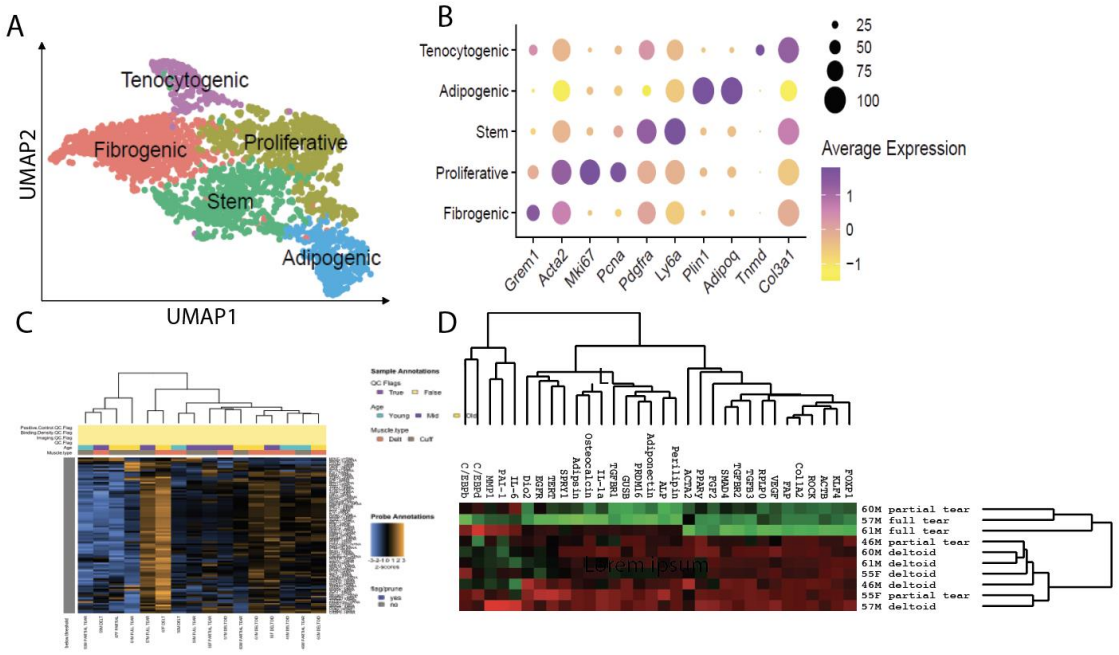
What's on the horizon?

How to Legally Offer Anti-Aging Treatments at Your Medical Spa

*Posted By **Administration**, Tuesday, May 7, 2019*

NO!!!!

- Regulation of stem cell/aging clinics
- Harnessing endogenous cells, patient specific treatments?
- Better studies, lack of financial incentive in studies
  - Would better study design lead to successful biologic strategies or do we need a different strategy?
- **What do we do at UCSF?**
  - Orthopedic Regenerative Center
  - Research—how/why some treatments works
  - Inform patients of the evidence
  - Starting September 2021
  - Email me brian.feeley@ucsf.edu
  - Follow us: 6to8weeks podcast, @drbrianfeeley




Thank you