
Orthobiologics 2.0: 4 Keys to success



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Disclosures

- No relevant disclosures for this presentation



Objectives:

Challenges and variations with PRP



Understand not all PRP is the same



Data Collection and Future Trends



Treatment as a Functional Unit



Biologics: A paradigm shift in modern medicine

Lanny L. Johnson M.D. (MI, USA) : Arthroscopy 1970's

Lucio Buratto (Italy) M.D. : Lasik 1989

“Ignore, Criticize, and Imitate”

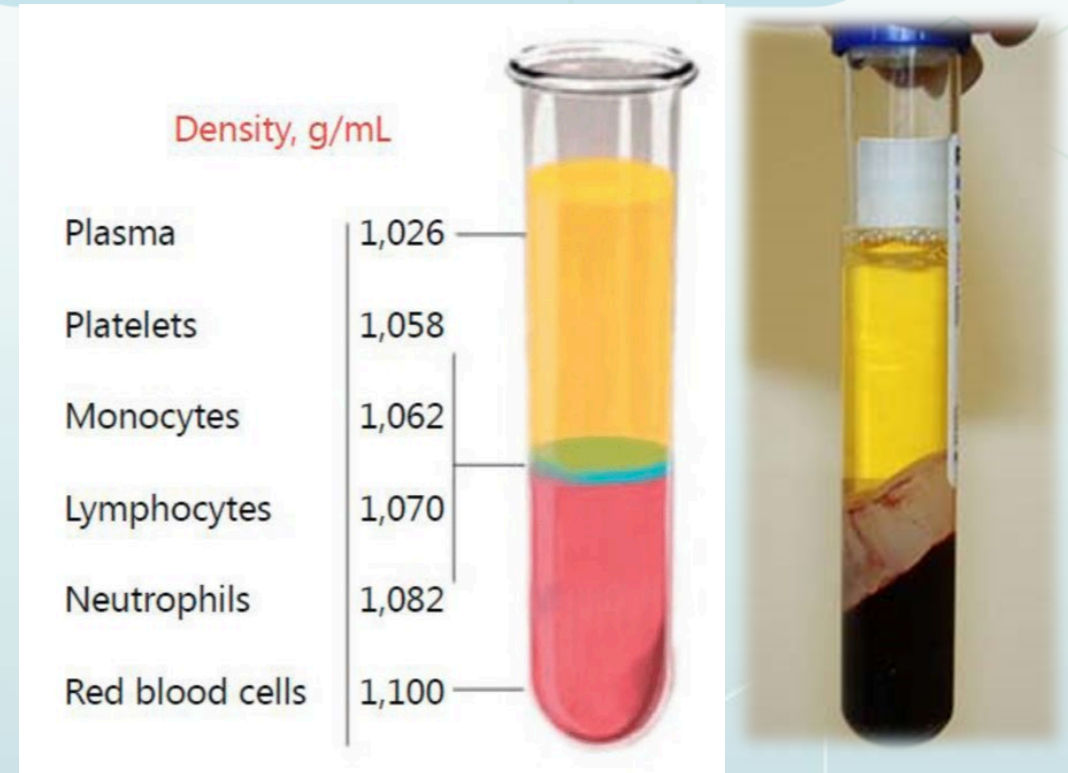
PRPs Generalized Mechanism of Action:

Delivery of Supra-physiologic GF's to stimulate the body's inherent ability to self heal.



What is Platelet Rich Plasma?

- Concentrated cellular milieu of GF from a patient's venous blood following centrifugation
- The autologous platelet concentration must be above baseline
 - Gen varies between 1.5-15x

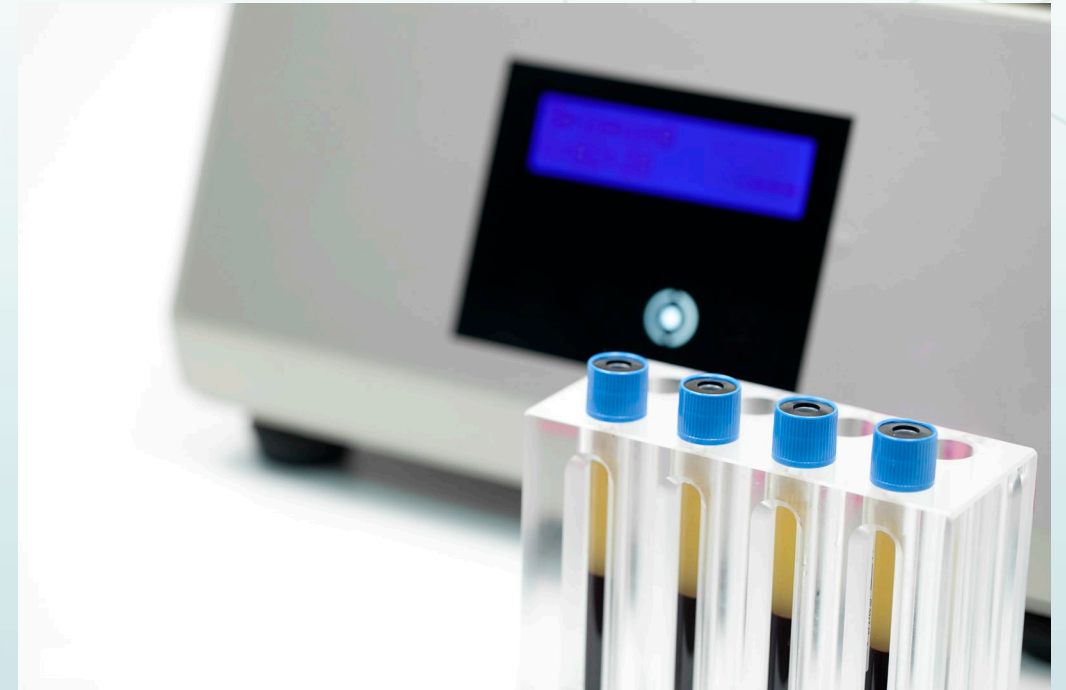


(Alves 2014)

PRP >1500 Cellular Components! Variation in cell prep

Platelets contain:

- Alpha granules
 - GF, cytokines, antibacterial proteins, protease inhibitors, adhesion molecules, coagulation factors, and fibrinolytic factors
- Dense granules
 - adenosine diphosphate (ADP) and adenosine
- Lysosomal granules
 - contain glycohydrolases
- Mitochondria
 - serotonin, histamine, dopamine and catecholamine, ATP, and calcium ions



Yes! But No?? Concentration & study design matters.



AJSM: A single autologous PRP injection combined with rehabilitation was significantly more **effective** in treating hamstring injuries vs rehabilitation alone.

Am J Sports Med. 2014 Oct;42(10):2410-8. doi: 10.1177/0363546514541540. Epub **Jul 29 2014**



NEJM: **no benefit** for intramuscular PRP injections, compared with placebo injections, with acute hamstring injuries. N Engl J Med 2014; 370:2546-2547 DOI: 10.1056/NEJMc1402340

June 26 2014



Supplement to:

PM&R

*The journal of injury, function
and rehabilitation*

**PHYSIATRIC APPLICATIONS OF STEM CELL THERAPIES
IN REGENERATIVE TREATMENTS OF MUSCULOSKELETAL
CONDITIONS**

The Official Journal of the
American Academy of
Physical Medicine and Rehabilitation

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PRP classifications:

There is significant variability in PRP preparation and cellular composition. PRP classifications have attempted to standardize reporting.

Main PRP Classification Systems:

- PLRA

[Kenneth Mautner¹](#), [Gerard A Malanga²](#), [Jay Smith³](#), [Brian Shiple⁴](#), [Victor Ibrahim⁵](#), [Steven Sampson⁶](#), [Jay E Bowen⁷](#)

- MARSPILL (Lana et al 2017)



EXPERT OPINION

ON BIOLOGICAL THERAPY

Platelet-rich plasma for the treatment of knee osteoarthritis: an expert opinion and proposal for a novel classification and coding system

Elizaveta Kon^{1,2}, Berardo Di Matteo^{1,2,3}, Diego Delgado⁴, Brian J Cole⁵, Andrea Dorotei^{1,2}, Jason L Drago⁶, Giuseppe Filardo⁷, Lisa A Fortier⁸, Alberto Giuffrida^{1,2}, Chris H Jo⁹, Jeremy Magalon^{10,11}, Gerard A Malanga¹², Allan Mishra¹³, Norimasa Nakamura¹⁴, Scott A Rodeo¹⁵, Steven Sampson¹⁶, Mikel Sánchez^{4,17}

Expert Opin Biol Ther Dec 2020.

PLRA

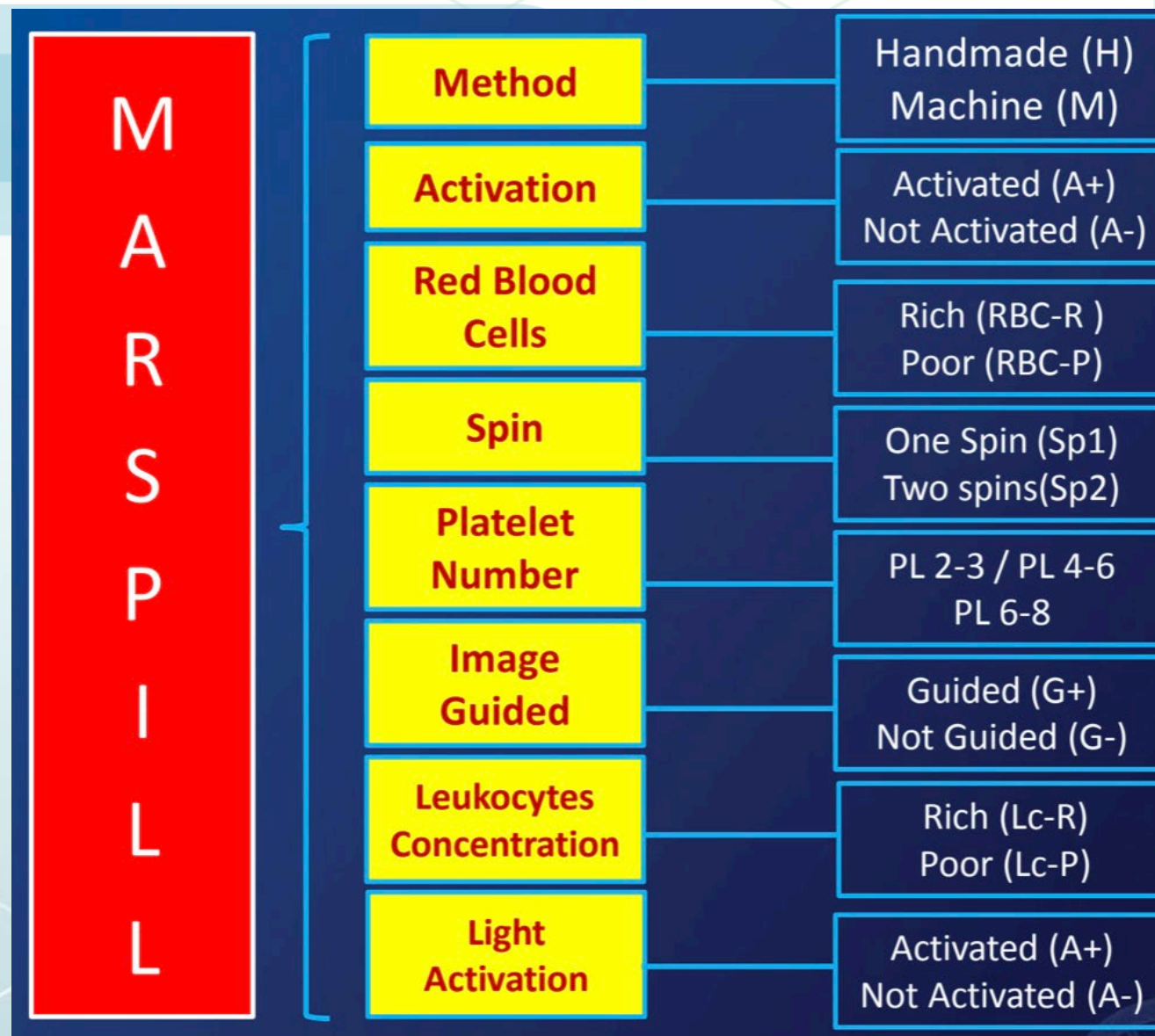
Mautner et al. 2015

		Criteria	
P	Platelet count	$\frac{\text{---}}{\text{Volume}}$	$\frac{\text{---}}{\text{Concentration/ uL}} \text{M}$
L	Leukocyte Concentration	>1%	+
		<1%	-
R	Red Blood Cell Concentration	> 1%	+
		< 1%	-
A	Activation	Yes	+
		No	-



MARSPILL

Lana et al 2017



As presented at TOBI 2018

Does PRP Formula Matter?



The effect of platelet-rich plasma formulations and blood products on human synoviocytes: implications for intra-articular injury and therapy

- Dragoo et al. AJSM 2014

- Results:
 - Treatment of synovial cells with **LR-PRP and RBCs resulted in significant cell death and proinflammatory mediator production**
- Recommendations based on the paper:
 - Clinicians should consider using **leukocyte-poor, RBC-free formulations of PRP when administering intra-articularly**



Haemophilic Arthropathy Inflammation & Joint Destruction

Hemoglobin releases Iron (hemosiderin) that deposits in synovium causing catabolic state

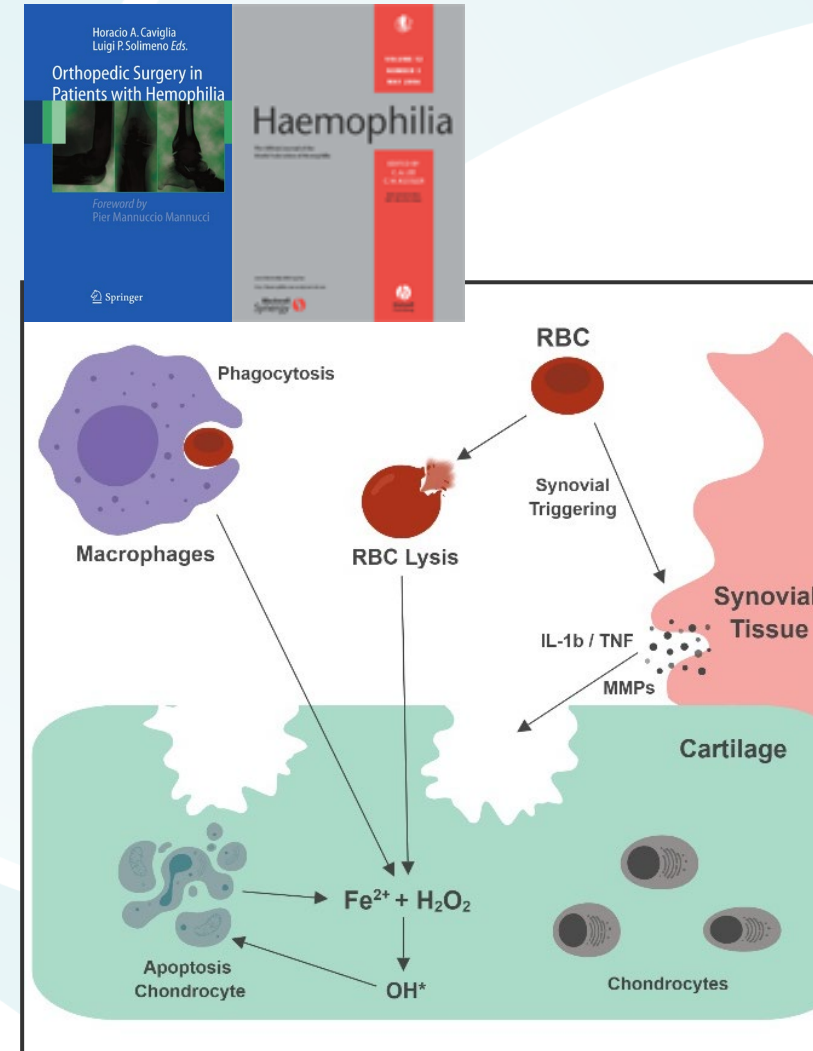
Damaged RBC's increase free radicals via monocyte/macrophage IL-1

Causes chondrocyte apoptosis

4 day exposure of human cartilage to haemarthrosis: decreases proteoglycan content (cartilage matrix)

Beagle dogs injected with autologous blood 2x/wk for 4 wks. 10 wks later.. joint damage was seen in those that were allowed to weight bear.

Hooiveld et al. Haemoglobin-derived iron-dependent hydroxyl radical formation in blood-induced joint damage: An in vitro study. [Rheumatology](#) 42(6):784-90 · June 2003
Hooiveld et al. Joint Damage as a Result of Hemarthrosis. Springer. 2008.
G. Roosendaal et al. Pathogenesis of Haemophilic Arthropathy. 27 April 2006
<https://doi.org/10.1111/j.1365-2516.2006.01268.x>



Recently Published RTCs With Methods Concerns

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, David B. Merkow,[†] BA, Kyle Pilz,^{†¶} MMS, PA-C, and Lisa A. Fortier,^{**} DVM, PhD, DACVS
Investigation performed at the Rush University Medical Center, Chicago, Illinois, USA

The American Journal of Sports Medicine, Vol. 45, No. 2
DOI: 10.1177/0363546516665809
© 2016 The Author(s)

In-Depth 5-in-5

Efficacy of Platelet-Rich Plasma for the Treatment of Interstitial Supraspinatus Tears

A Double-Blinded, Randomized Controlled Trial

Adrien J. Schwitzguebel,^{*†} MD, Frank C. Kolo,[‡] MD, Jérôme Tirefort,^{*} MD, Abed Kourhani,[§] MD, Alexandra Nowak,[†] MD, Vincent Gremeaux,[†] MD, PhD, and Alexandre Lädermann,^{*§#} MD
The American Journal of Sports Medicine 2019;47(8):1885–1892
DOI: 10.1177/0363546519851097
© 2019 The Author(s)
Journal of Orthopaedics and Trauma Surgery

Original Research

Bone Marrow Aspirate Concentrate Is Equivalent to Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis at 1 Year

A Prospective, Randomized Trial

Adam W. Anz,^{*†} MD, Ryan Hubbard,[†] MD, Nicole K. James R. Andrews,[†] MD, and Joshua G. Hackel,[†] MD

Investigation performed at the Andrews Research & Education Foundation, Gulf Breeze, Florida, USA

The Orthopaedic Journal of Sports Medicine, 8(2), 2325967119900958
DOI: 10.1177/2325967119900958
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What About the Methods Used?

Need for Proper Classification of PRP: Letter to the Editor

DOI: 10.1177/0363546517693989

Efficacy of Platelet-Rich Plasma for the Treatment of Interstitial Supraspinatus Tears: Letter to the Editor

DOI: 10.1177/0363546519879424

The Orthopaedic Journal of Sports Medicine, 8(10), 2325967120960706
DOI: 10.1177/2325967120960706
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The American Journal of Sports Medicine, Vol. 45, No. 6
© 2017 The Author(s)

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Stanford, California, USA

Bone Marrow Aspirate Concentrate Is Equivalent to PRP for the Treatment of Knee OA at 1 Year: Letter to the Editor

The American Journal of Sports Medicine
2020;48(1):NP8–NP10
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Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis. RESTORE Randomized Clinical Trial. (Nov 2021)

- 288 patients w/ Mild to Moderate OA
 - PRP vs Saline
 - 3 injections
 - 12 mo f/u
-
- IA PRP compared Vs saline placebo, did not result in a significant difference in symptoms or joint structure at 12 months. These findings do not support use of PRP for the management of knee OA.
 - Baria et al response to editor: Plt conc 1.2x baseline and some may be below baseline w/ standard deviation.
 - Possible dose too low for clinical response; dose response curve has been established.
 - Title should have been plasma vs placebo for knee OA.
-
- JAMA. 2021;326(20):2021-2030. doi:10.1001/jama.2021.19415
 - JAMA March 22/29, 2022 Volume 327, Number 12

Regenerative Medicine Landscape: Bad Actors & Liability. Why Data is EVEN MORE Important Now!

News & Analysis

Medical News & Perspectives

Unproven but Profitable: The Boom in US Stem Cell Clinics

Rita Rubin, MA

Short Communication

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Regenerative Medicine

Rapid change of a cohort of 570 unproven stem cell clinics in the USA over 3 years

Paul S Knoepfler^{*,1,2}

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²Institute of Pediatric Regenerative Medicine, Shriners Hospital for Children Northern California, Sacramento, CA 95817, USA
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Letters

RESEARCH LETTER

Characteristics and Scope of Training of Clinicians Participating in the US Direct-to-Consumer Marketplace for Unproven Stem Cell Interventions

[FREE STEM CELL EVENT] (no more than a few minutes from you)- you will be able to learn about stem cells from the work of pioneers in the field of Stem Cell Therapy.

Stem Cell Therapy may REPAIR & REBUILD cartilage in joints, while reducing pain and inflammation all WITHOUT SURGERY!

It's true... Stem Cell Therapy HAS changed THOUSANDS of our patients lives.

On Tuesday, we will be bringing you our doctors stories, and share how you can get stem cell therapy right here in [redacted] Simply click here for dates, locations

Bertucci's



STEM CELLS

TRANSLATIONAL AND CLINICAL RESEARCH

Medicine on the Fringe: Stem Cell-Based Interventions in Advance of Evidence

ALAN C. ROSENBERG,¹ LAUREN A. HUTCHINSON,² BENJAMIN SCHONBERG,² DEBRA J. H. MATTHEWS²

¹Johns Hopkins Berman Institute of Bioethics, Johns Hopkins University, Baltimore, Maryland, USA; ²The London School of Hygiene and Tropical Medicine, University of London, London, United Kingdom; ³Boston University, Boston, Massachusetts, USA

Key Words: Stem cells • Therapy • Bioethics • Clinical trial

THE HEALING MIRACLE



12 WAYS TO ELIMINATE CHRONIC PAIN WITH STEM CELLS

REPORT OF THE FSMB WORKGROUP TO STUDY REGENERATIVE AND STEM CELL THERAPY PRACTICES

Report

THE PEW CHARITABLE TRUSTS

Oct 2019

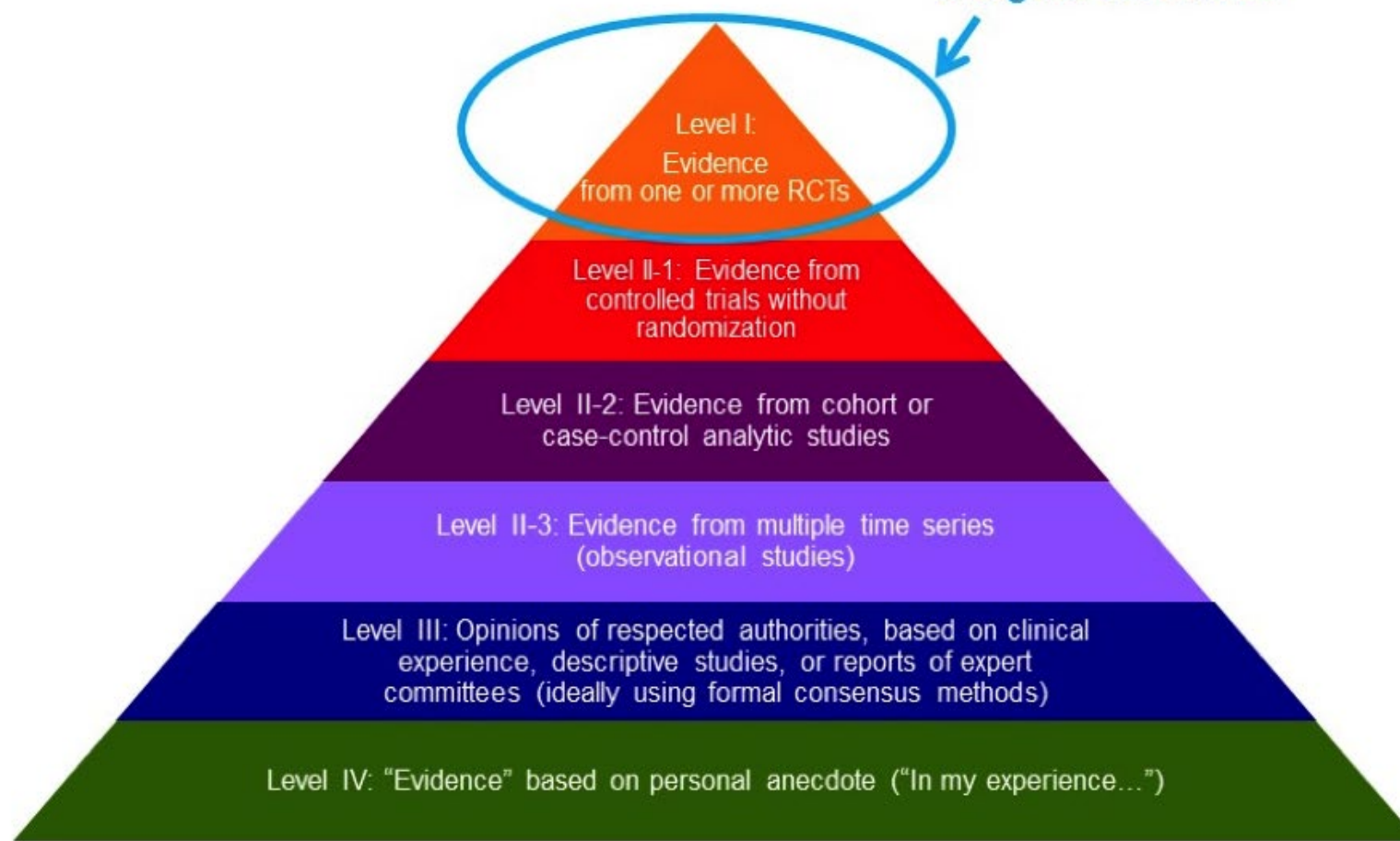


FDA's Framework for Regulating Regenerative Medicine Will Improve Oversight

Further action needed to facilitate development of safe, effective treatments

Levels of Evidence

Randomized Controlled
Trials (RCTs)
“the gold standard”



Level 1 data on PRP

Lateral epicondylitis: Common extensor tendinosis / tennis elbow (AJSM)

Mild to moderate knee OA (mult journals)

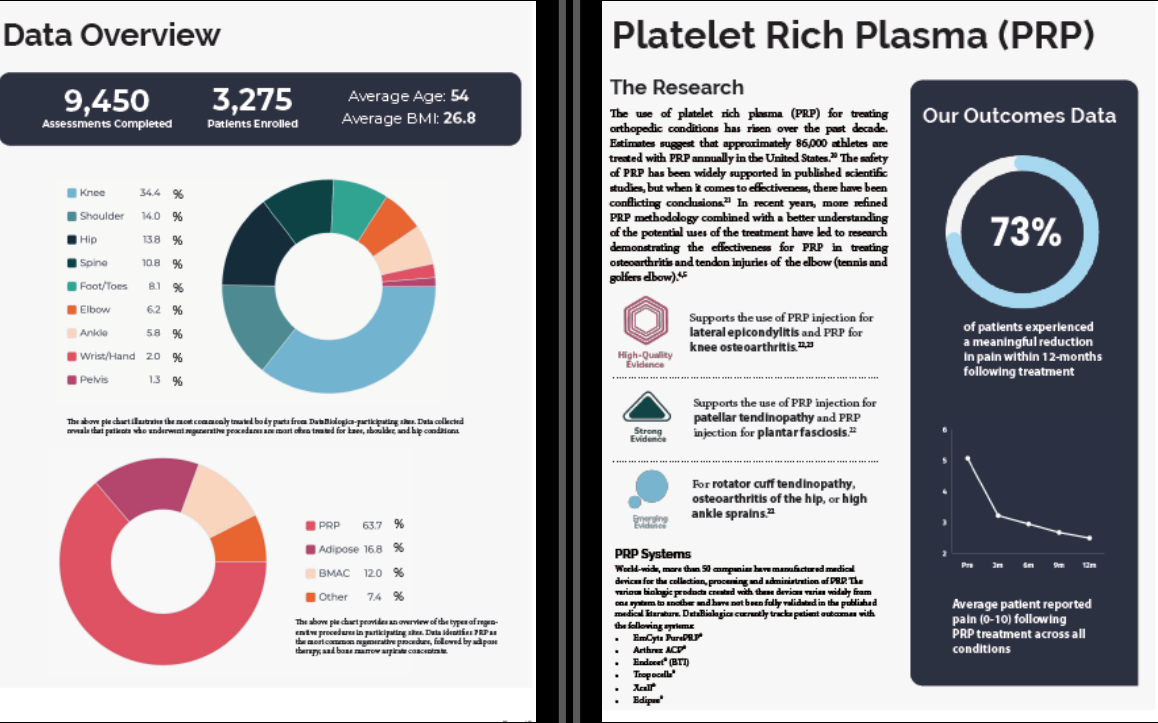
Plantar Fasciitis (AJSM)

Gluteal Tendinosis (AJSM)



Our Analysis

The above outcomes data seems to show that good outcomes can be obtained from both PRP and adipose tissue based treatments for the treatment of knee conditions such as knee osteoarthritis. This information should be used with caution as there are several differences among the treatment groups. For example, the use of PRP or adipose tissue based treatments depends upon the unique characteristics of a patient's condition. Therefore, while this data is useful for demonstrating the general efficacy of a given treatment option, meaningful inferences will require the collection of specific data for unique patient populations.



What we track

Patient Reported Outcomes

Adverse Events
FAAM
HOOS Jr.
KOOS Jr.
Neck Disability Index
Oswestry Disability Index
Pain Scale (NPRS)
PHQ-4
QuickDASH
VISA-A

Body Parts

Ankle
Cervical Spine
Elbow
Foot/Toes
Hip
Knee
Lumbar Spine
Pelvis
Shoulder
Thoracic Spine
Wrist/Hand

Treatments

Adipose (MFAT)
Bone Marrow
Hyaluronic Acid
Perinatal Tissue
Platelet Lysate
Platelet Poor Plasma (A2M, PPC)
Platelet Rich Plasma (PRP)
Prolotherapy
Shock Wave Therapy (ESWT/EPAT)
Sonex
Tenex

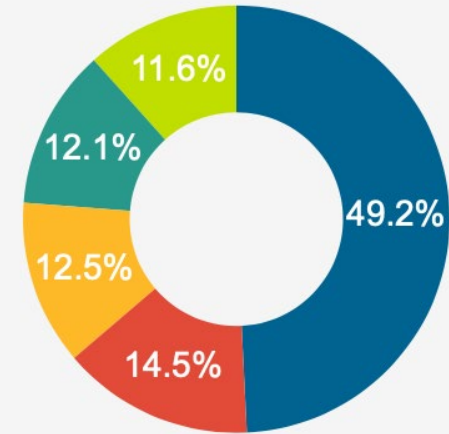
9,423

Assessments Completed

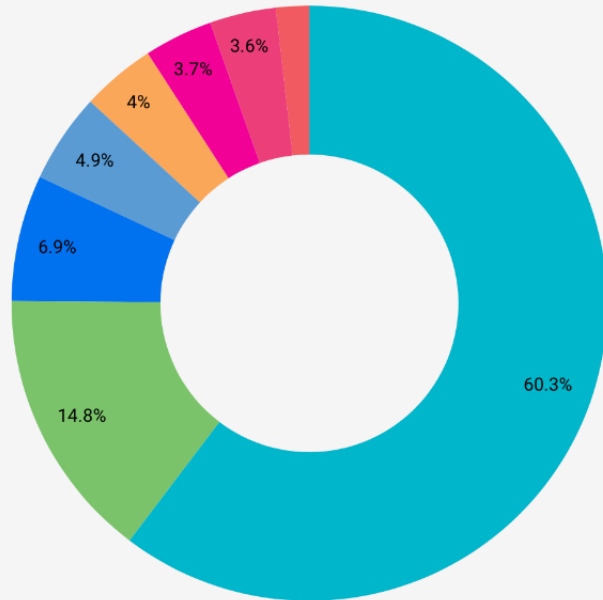
3,252

Patients Enrolled

Average Age: **54**
Average BMI: **26.8**

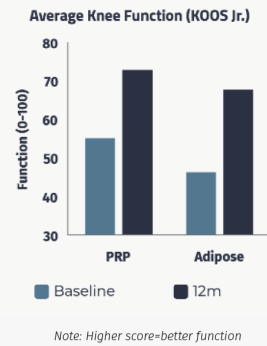
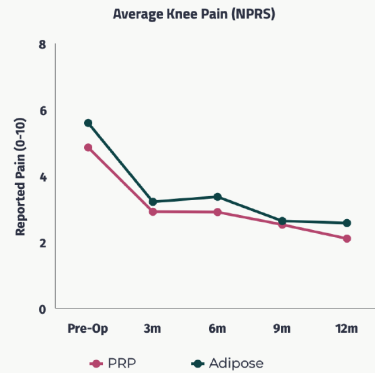


● Knee Osteoarthritis ● Shoulder Osteoarthritis
● Shoulder Tendon Tear (partial thickness)
● Shoulder Tendinosis ● Lumbosacral Facet Joint Osteoarthritis



● PRP
● Adipose
● Bone Marrow
● SuperShot PRP/BMC
● Other
● Shockwave Therapy
● Percutaneous Tenotomy
● Hyaluronic Acid

Data Overview



Report for Knee Pain

Our Analysis

The above outcomes data seems to show that good outcomes can be obtained from both PRP and adipose tissue based treatments for the treatment of knee conditions such as knee osteoarthritis. This information should be used with caution as there are several differences among the treatment groups. For example, the use of PRP or adipose tissue based treatments depends upon the unique characteristics of a patient's condition. Therefore, while this data is useful for demonstrating the general efficacy of a given treatment option, meaningful inferences will require the collection of specific data for unique patient populations.

New Trends: Wearables, Remote Monitoring, PROMS (Patient Reported Outcome Measures)

Growth fueled by:

- Increased Patient Involvement in Their Treatment Choices
- Mounting Evidence Wearables Lead to Improved Patient Care
- Provides cost effective access and reporting

Novel assessment of leukocyte-rich platelet-rich plasma on functional and patient-reported outcomes in knee osteoarthritis: a pilot study

- 12 patients
- US guided 10ml LR-PRP as **assessed by functional and patient-reported outcomes** at early time points (6 weeks)
- First study integrating **wearable technology** and patient-reported outcomes.
- PRP demonstrated significant improvement in timed up and go (TUG), pain and quality of life scales and balance parameters



Functional Unit Approach w/ image guidance!

Extraarticular

Intraarticular

Subchondral Bone

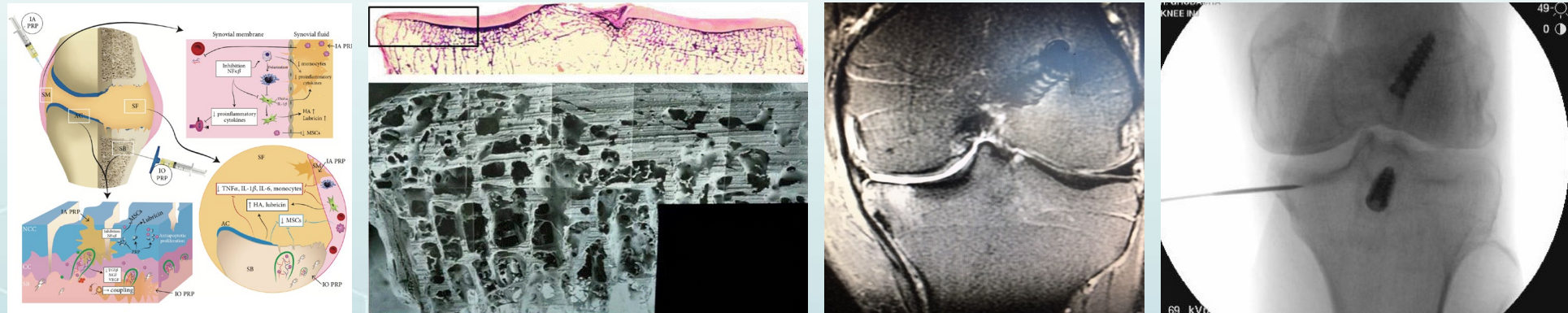
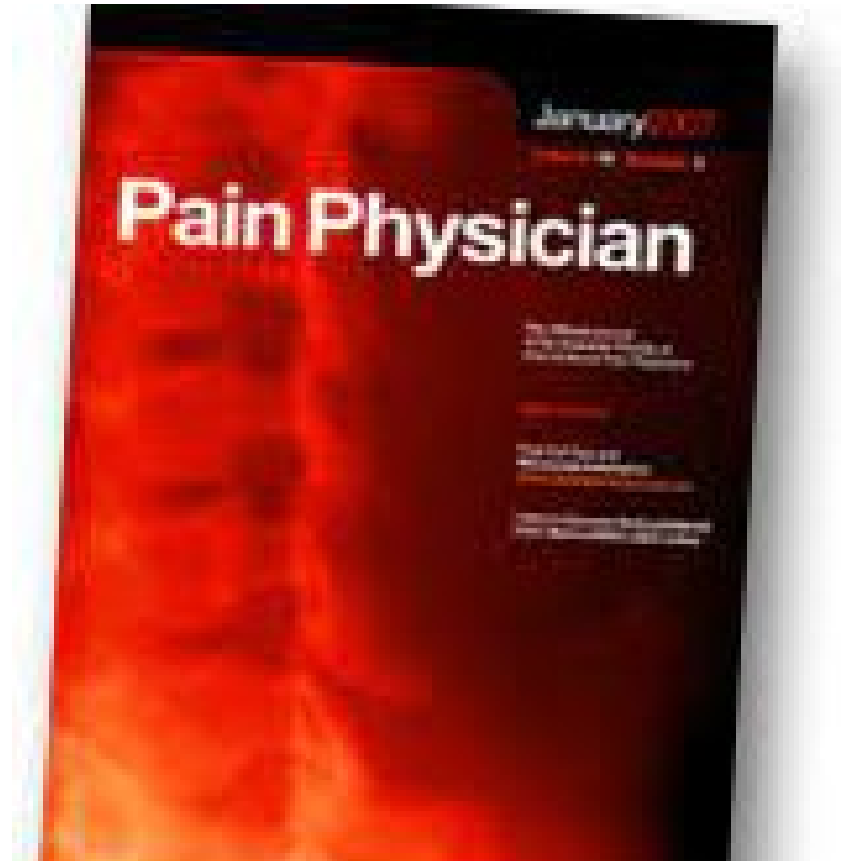


Image courtesy of Henning Madry, Homburg Germany

Evaluation of the Effectiveness of Autologous Bone Marrow Mesenchymal Stem Cells in the Treatment of Chronic Low Back Pain Due to Severe Lumbar Spinal Degeneration: A 12-Month, Open-Label, Prospective Controlled Trial. (Mar 2022)

- Zaynab Syed, ., Divit Jain, ., Meghana Ganjam, ., Zaid Syed, ., Pavan Yerramsetty, MD, Navneet Boddu, MD, Vivek Manocha, MD, Sachi Bhati, ., Kwadwo Boachie-Adjei, BS, CPH, Jessica Herrera, BS, Ryan Dragella, PhD, **Sairam Atluri, MD**, Matthew B. Murphy, PhD, Nikhil Grandhi, ., and **Laxmaiah Manchikanti, MD**
- BMC injection into discs, facets, spinal nerves, and SIJ with conventional tx, Vs control of NSAIDs, OTC drugs, exercise /PT, spinal injections and opioids.
- TNC, CFUs, CD34-+ markers and platelets were recorded + post-procedure MRI changes
- 1st controlled study BM-MSCs in severe degenerative spine disease targeting multiple structures.
- Improved function & Reduced Opioids in tx group at 12 mo



Conclusion: 4 keys to success

01

Cell prep matters! Choose wisely and critically review PRP studies

02

Integrate quality control with PRP analysis

03

Track your outcomes data

04

Treat the structure as a functional unit



ASIPP @ TOBI 2022 Partnership: Spine Session + Hands on Spine Cadaver Lab w/ Cert and practice accelerator workshop

Role of ASIPP in the Growth of Regenerative Medicine: What Can ASIPP Do For You | Laxmaiah Manchikanti, MD

Certification in Regenerative Medicine: Do You Need It? Pathway for Certification | Annu Navani, MD

PRP in Low Back Pain: What's the Current Evidence? | Shelly Jordan, MD

BMAC in Low Back Pain: What Does The Evidence Say? | Sheri Albers, DO

Recent Advances and Future Directions of Intradiscal Biologic Therapies | Annu Navani, MD

Ask Anything: ASIPP @ TOBI – Interventional Spine Panel Discussion and Q&A | Laxmaiah Manchikanti, MD; Annu Navani, MD; Shelly Jordan, MD; Sheri Albers, DO



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Questions?

