Bone Marrow Aspirate Concentrate (BMAC) Procedure for Knee Osteoarthritis in Obesity

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Mercy Health – Cincinnati SportsMedicine and Orthopaedic Center

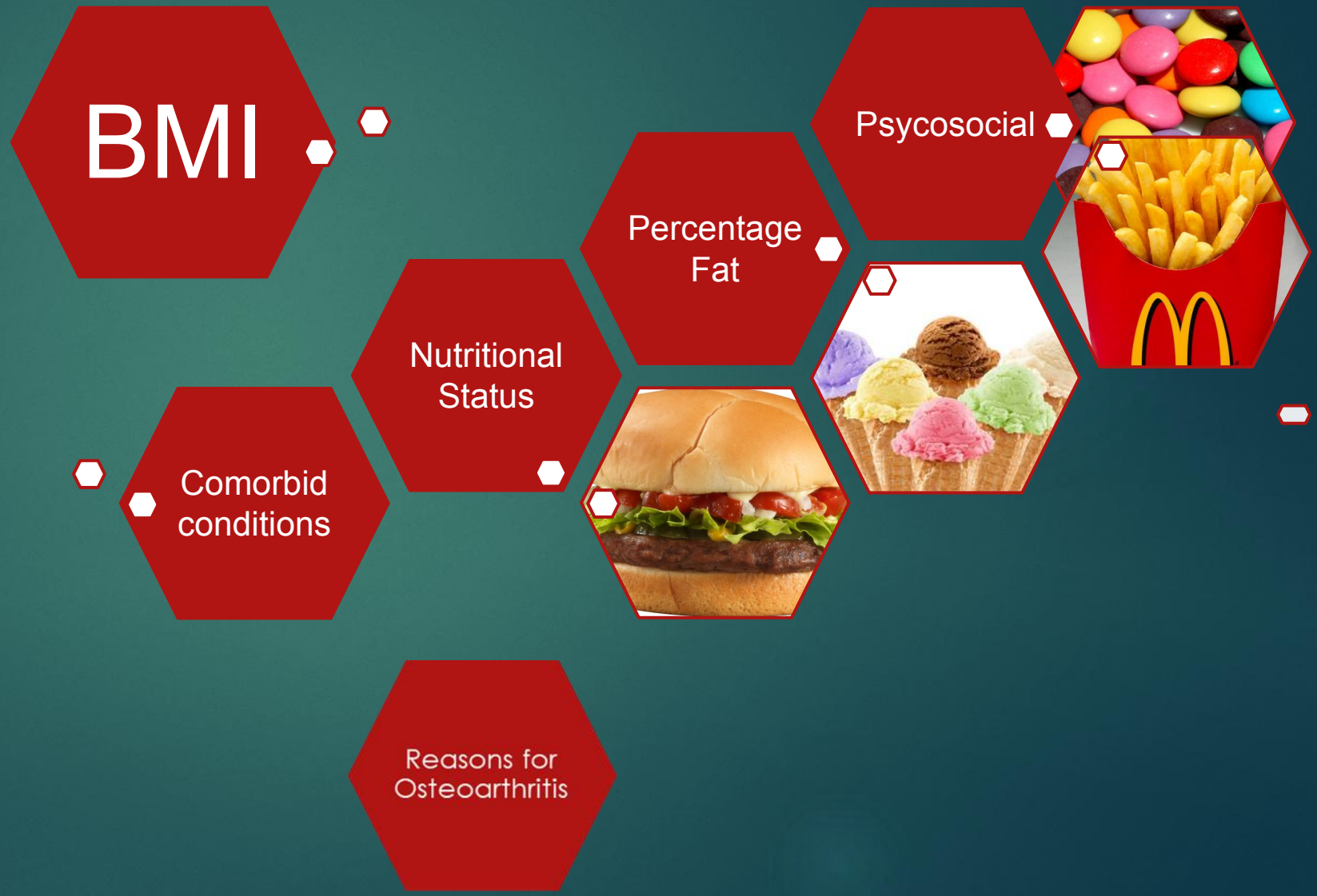
BEFORE REGEN CENTER

AFTER REGEN CENTER


BEFORE PROLOTHERAPY
2005
DECREASED JOINT SPACE WIDTH
AFTER PROLOTHERAPY
2007
INCREASED JOINT SPACE WIDTH

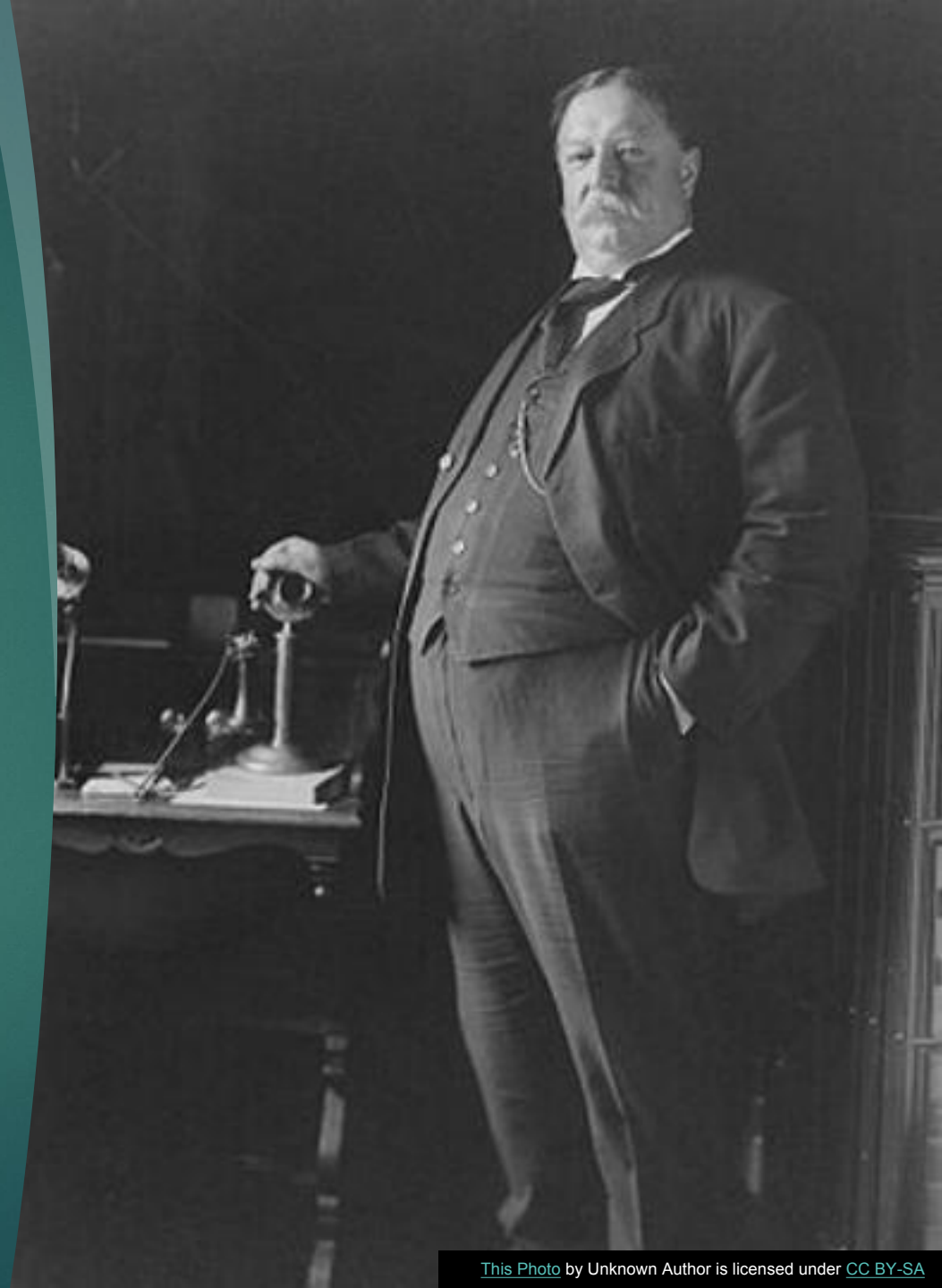
Treatment of arthritis in the obese patient

- Who is your patient
  - BMI
    - Height /Weight
  - Percentage Fat
  - Nutritional Status
  - Reasons for Osteoarthritis
  - Co morbid conditions
  - Bio-psycho-social makeup



Treatment of Arthritis in the Obese Patient

- Why are they in your office?
  - Pain
  - Difficulty with Walking
  - Decrease in Functioning
  - Decrease in Activity
  - Frustration with ability to control their lives
    - ARE THESE RELATED TO ARTHRITIS OR OBESITY
  - Refused surgery by another physician



Treatment of Arthritis in the Obese Patient

- Options for treatment in the office
  - Steroid injection
  - Gel injection
  - Physical therapy
  - Occupational therapy
  - Bracing
  - TENS/NEMS
  - Medications--Topical /Oral
  - Narcotics
  - Nutritional Supplements
  - Acupuncture

Total knee in obese patient

- Risk ratios
  - Severe Obese
    - 3.17 % septic revision
  - Morbidly Obese
    - 9.75% septic revision
  - Super Obese
    - 7.22% septic revision
      - Ponnusamy, 2019

What can we offer?

BIOLOGIC AUGMENTATION

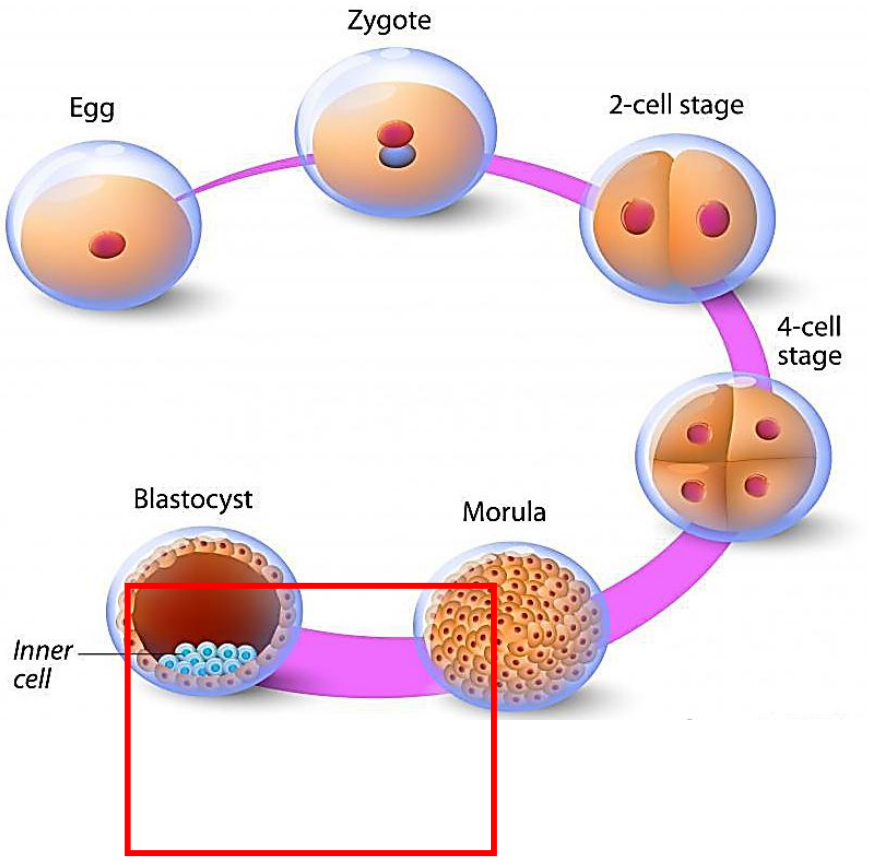
Relevance of Stem Cells

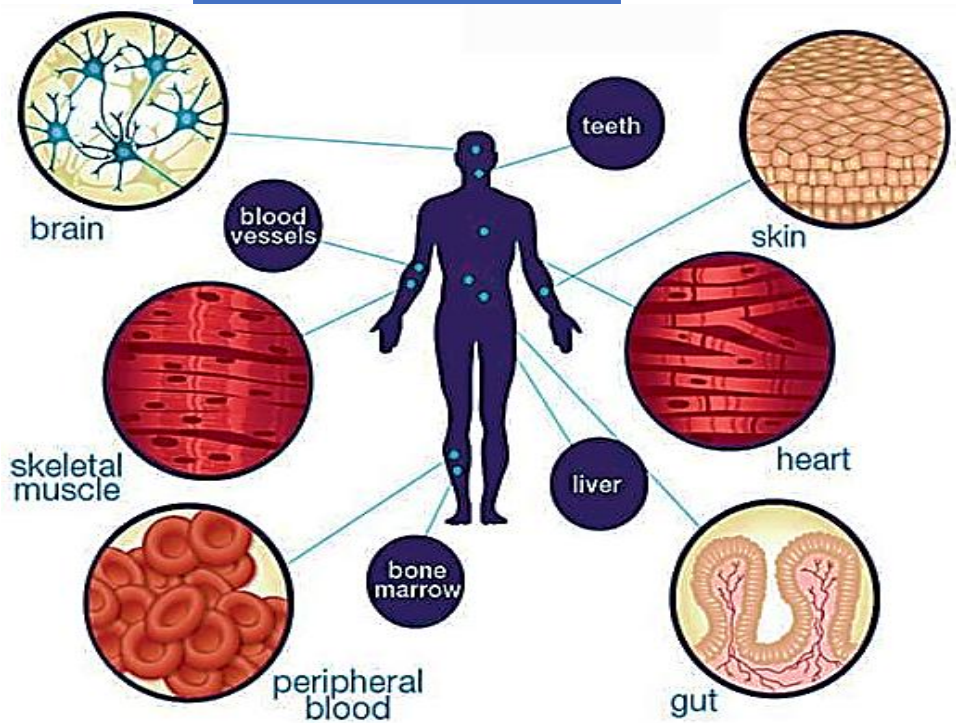
Stem Cells: Cells capable of differentiation and indefinite self-replication

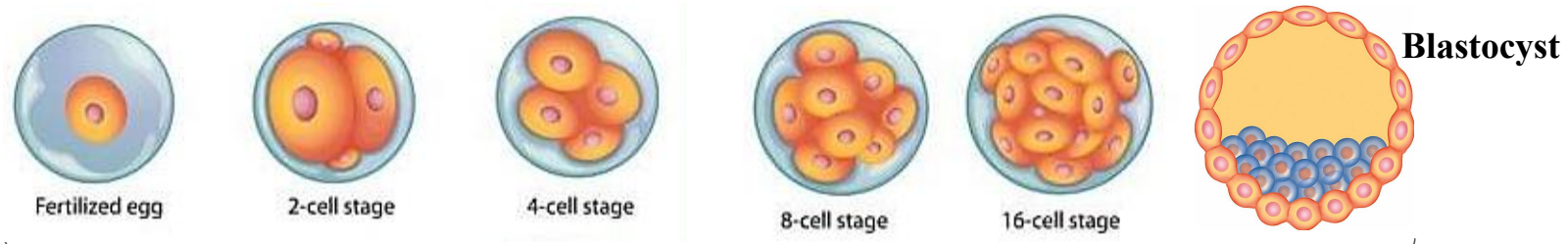
2 Types of Stem Cells

Embryonic: *Pluripotent* stem cells inside a blastocyst (post-implantation embryo)

Adult: *Multipotent* stem cells throughout body that replicate & differentiate to regenerate tissue





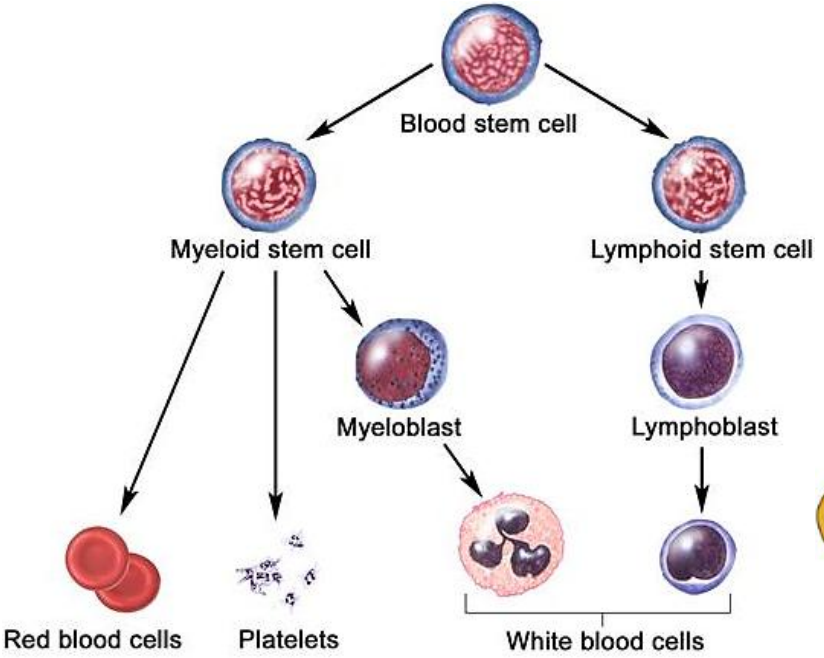


Totipotent Stem Cells → **Pluripotent Stem Cells**

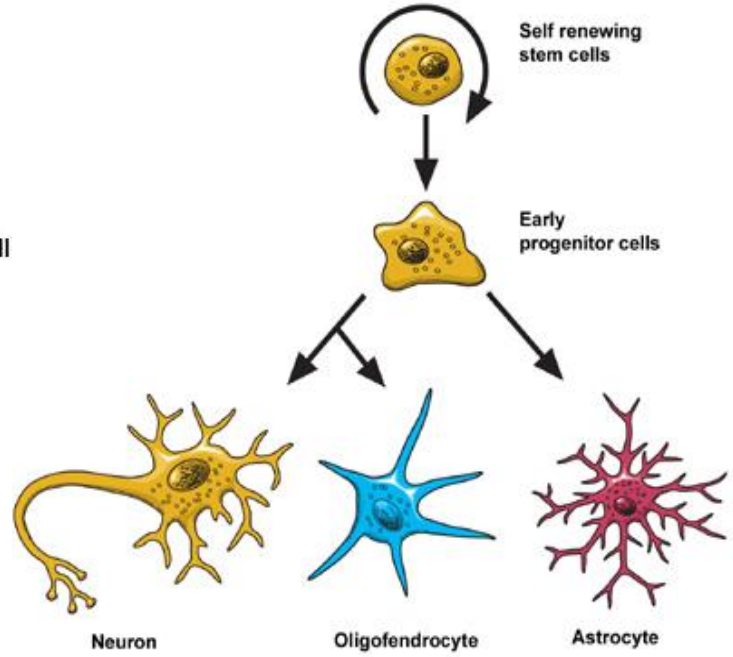
↓

Multipotent Stem Cells

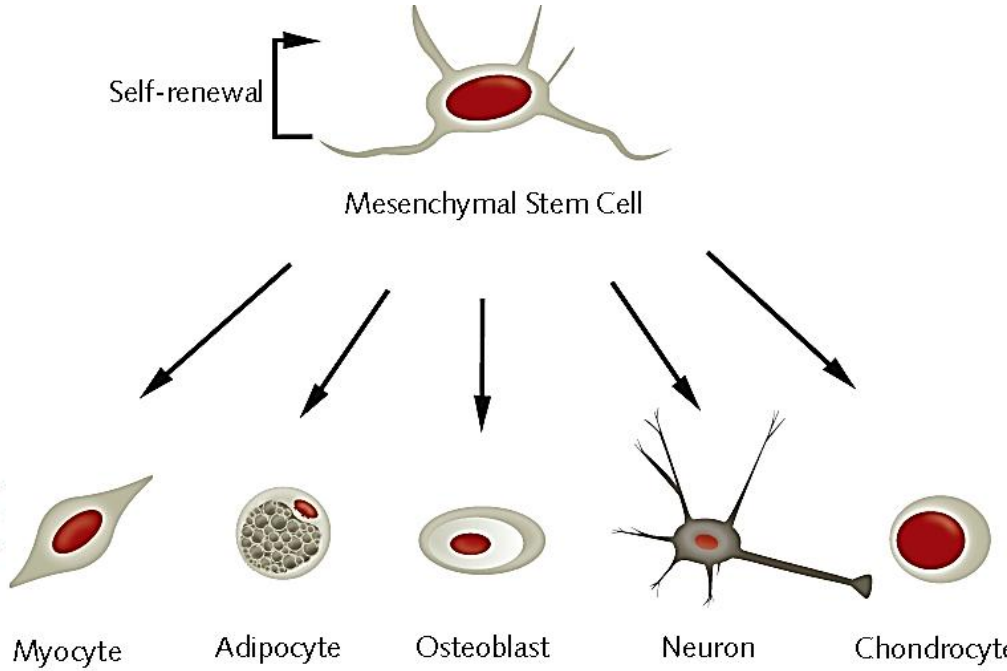
Hematopoietic Stem Cell

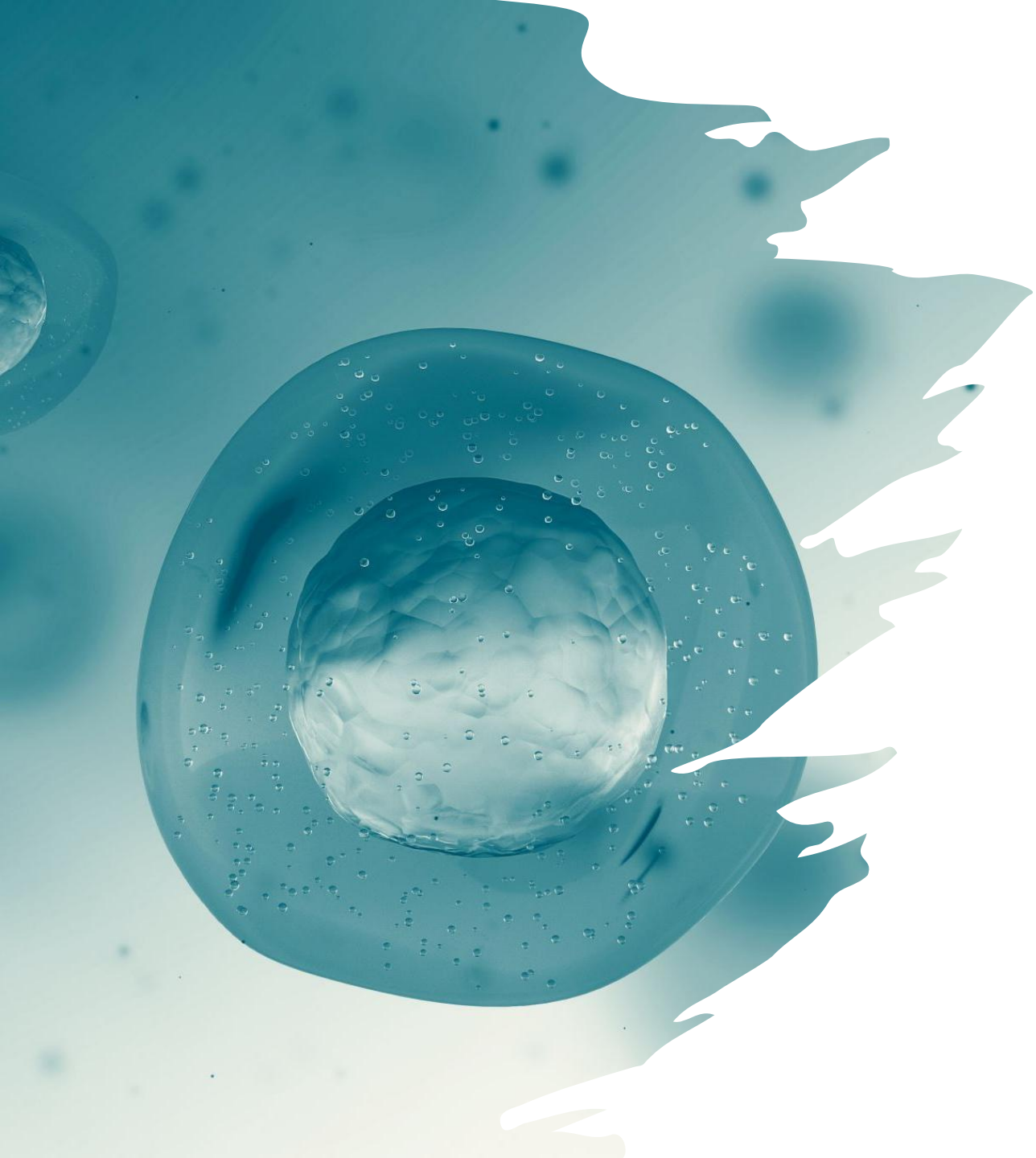


Neural Stem Cell



Mesenchymal Stem Cell





Stem Cells: Cells capable of differentiation and indefinite self-replication

<u>*Potency* Categories of Stem Cells</u>

1. **Totipotent stem cell**: Each cell can develop into *entire new organism*
2. **Pluripotent stem cells**: Each cell can differentiate into *any cell type*
3. **Multipotent stem cells**: Each cell can differentiate into *limited types of tissues*

What is the MSC?

- Mesenchyme is embryonic connective tissue that is derived from the mesoderm
- **Mesenchymal stem cells** are multipotent cells that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and adipocytes
- Adipose tissue is a rich source of MSCs (or adipose-derived mesenchymal stem cells, AdMSCs).

- MSCs do not differentiate into hematopoietic cells

What does the MSC Enable? Immunomodulation/Cell Communication

- Molecules having immunomodulatory effects
  - prostaglandin E2 (PGE2)
  - nitric oxide
  - indolamin 2,3-dioxigenase (IDO)
  - IL-6, IL-8, IL-10
- Surface markers - FasL,PD-L1 / 2
  - MAST CELLS, MACROPHAGES, T LYMPHOCYTES,B LYMPHOCYTES
  - NK CELLS

What else is the MSC doing?

- MSCs can produce antimicrobial peptides (AMPs)
  - human cathelicidin LL-37
  - β-defensines
  - lipocalin 2
  - Hepcidin

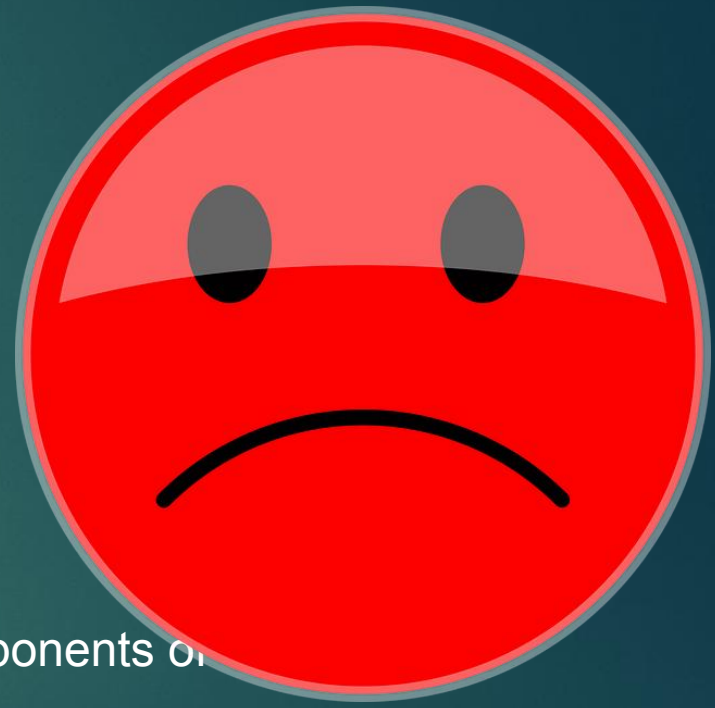
- Against Gram negative and Gram positive bacteria

What are the mediators? Exosomes?

- MSC differentiation into chondrocytes
  - TGF-β1–3; BMP-2, -4, -6, -7; fibroblast growth factor-2 (FGF-2); insulin-like growth factor-1 (IGF-1); insulin; and PTHrP
  - Adenosine 5'-triphosphate (ATP), stromal-derived factor-1β (SDF-1β), growth and differentiation factor-5 (GDF-5), FGF-18, TD-198946 and kartogenin (KGN)
- IL-1β effect on MSC differentiation into chondrocytes
  - Curcumin works against IL1
  - Hypoxic conditions and mechanical stress work against IL 1

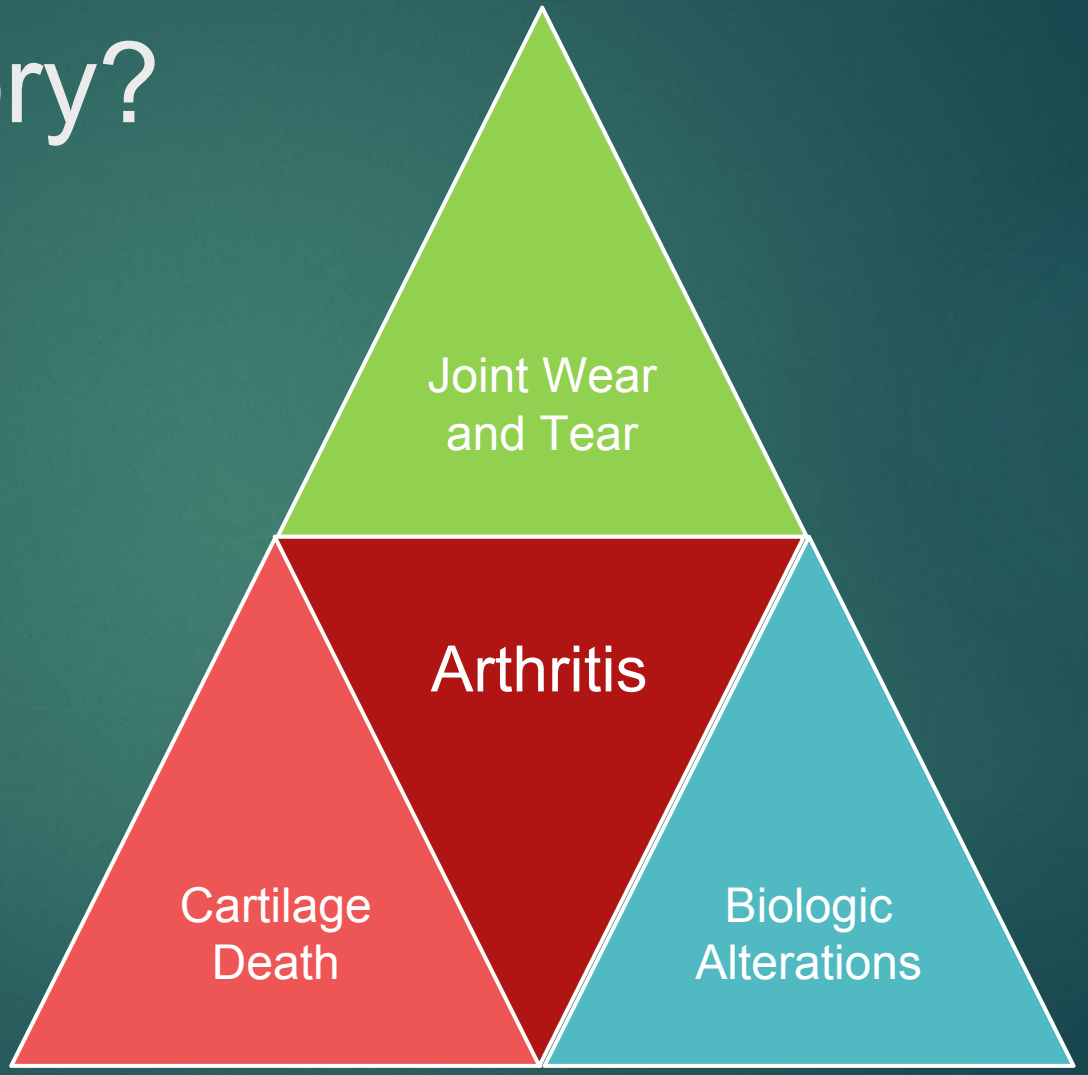
Proinflammatory Mediators

- IL-1
  - Proinflammatory cytokine
    - TNF, IL17
  - Inhibit chondrogenic differentiation
  - Induce apoptosis of chondrocytes
    - oxide (NO) and prostaglandin E2 (PGE2)
  - inhibit production of type II collagen and aggrecan, the major components of the cartilage matrix
  - increase the release of matrix metalloproteinases and aggrecanase, enzymes that degrade the matrices, resulting in cartilage destruction



How has arthritis changed in theory?

- Wear phenomenon
  - Trauma
  - Deformity
  - Congenital
- Cartilage Death
  - Cytokines
  - Factors
- Biologic Alterations
  - Inflammation positive
  - Inflammation negative
  - Cell mediatied responses

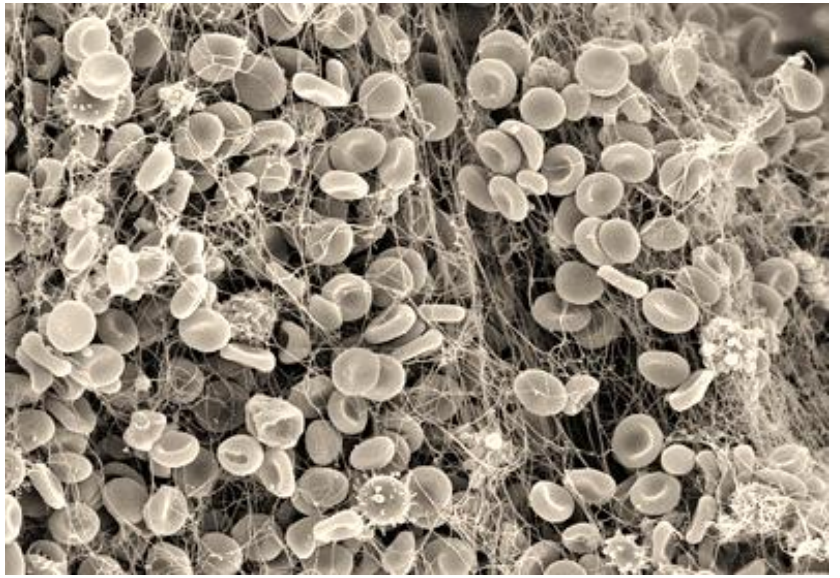


STEM CELL PROCEDURES

What is BMAC?

Bone Marrow

- Gelatinous hematopoietic tissue that resides within spongy/cancellous inner spaces of bone
- Comprised of progenitor cells, stromal cells (i.e. mesenchymal stem cells), growth factors, cytokines, platelets, etc.



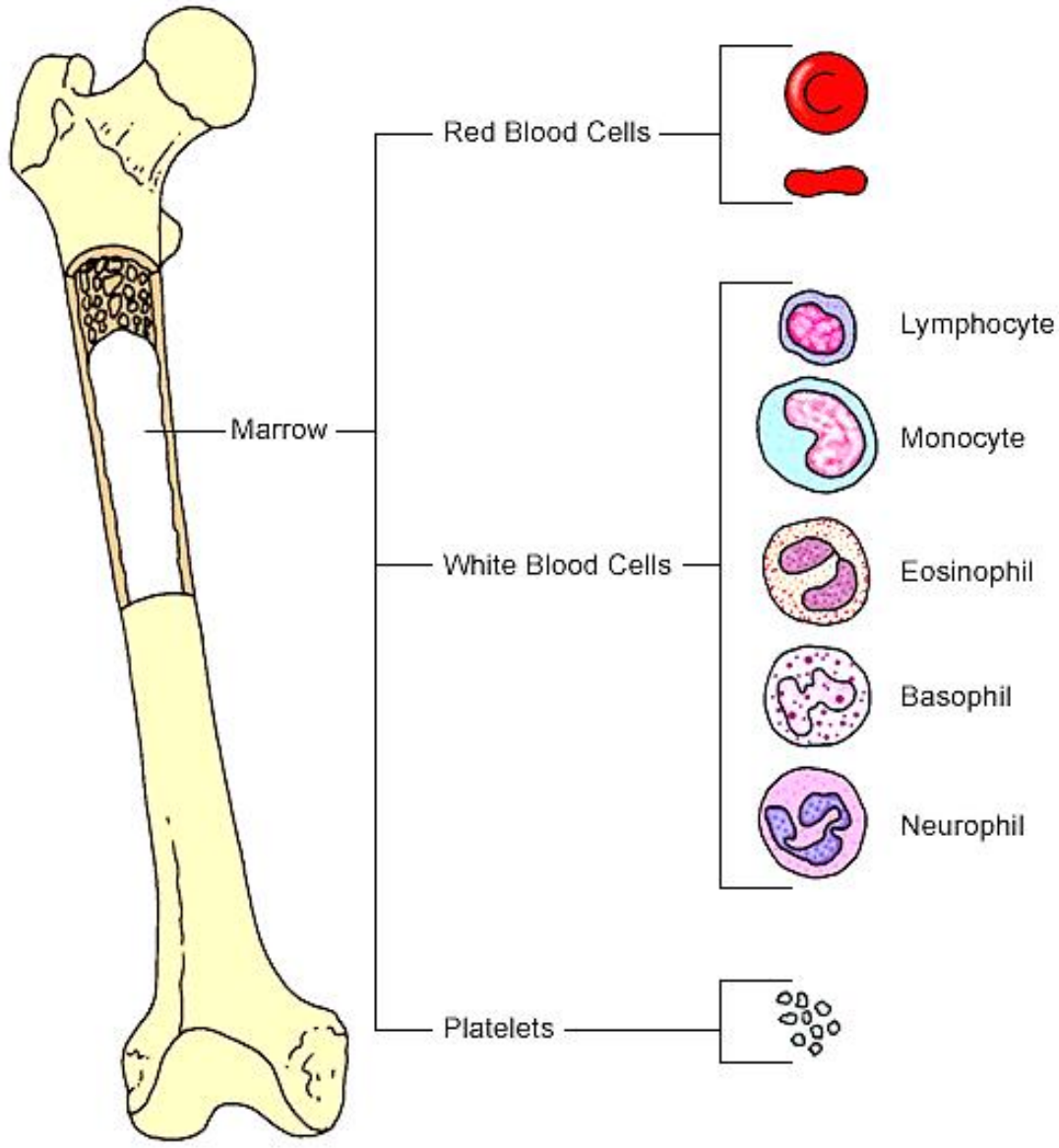
BMAC (Bone Marrow Aspirate Concentrate)

- Bone marrow harvested via aspiration and then centrifuged to concentrate marrow-derived nucleated cells, growth factors, cytokines and/or platelets

Contents of BMAC

Cellular Composition

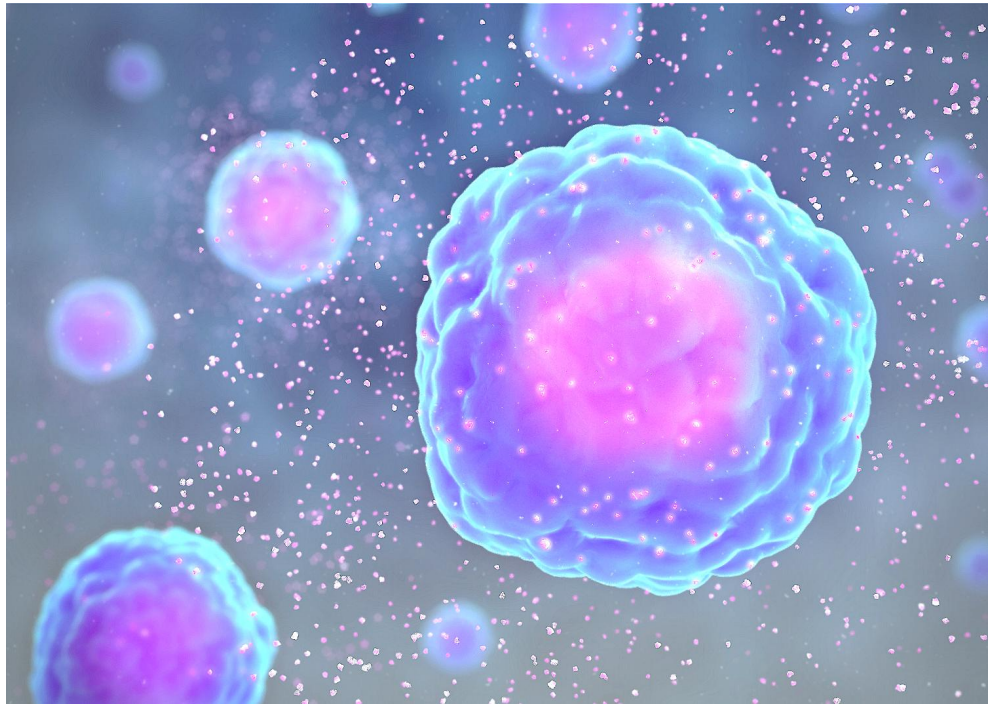
- **Erythroblasts** (28% in males, 23% in females)
- **Neutrophils** (33% in males, 37% in females)
- Lymphocytes (13%)
- Eosinophils (2%)
- Monocytes (1%)
- Basophils (0.1%)
- **Mesenchymal Stem Cells (0.001% to 0.01%)**
- **Platelets** (significant range)



Contents of BMAC

Cytokines and Growth Factors

- Platelet-derived growth factor (PDGF)
- Vascular endothelial growth factor (VEGF)
- Transforming growth factor – beta (TGF-b)
- Fibroblast growth factor (FGF)
- Bone morphogenetic protein (BMP) 2
- Bone morphogenetic protein (BMP) 7
- Insulin-like growth factor (IGF)
- Interleukins (IL-8, IL-1B, etc.)
- interleukin-1 receptor antagonist (IL-1RA)



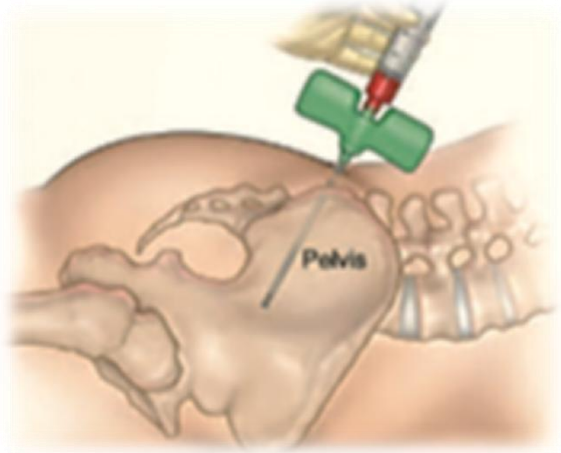
How BMAC is Obtained

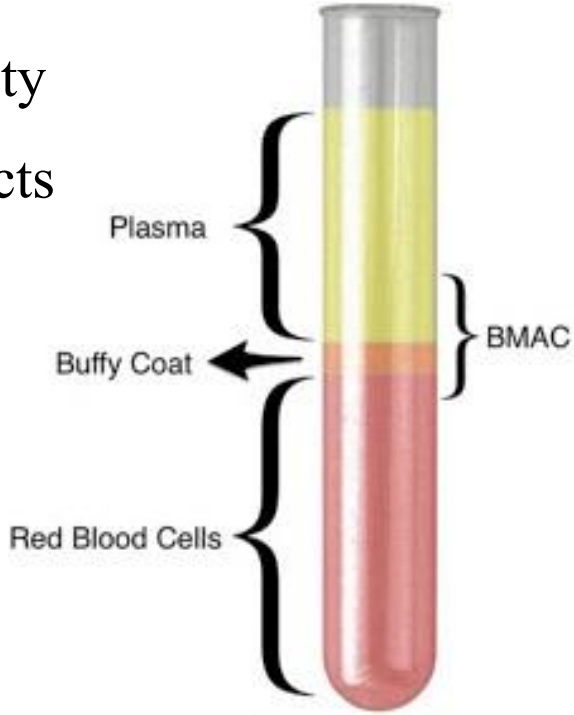
Harvesting Bone Marrow

- BMAC aspirated percutaneously from ASIS, Iliac crest, or PSIS using trochar, drill, and syringe

Processing Bone Marrow into BMAC

- Many systems available to harvest/process BMAC: All use centrifuge to separate RBCs, Platelets, nucleated cells, and serum proteins based on density
- Varying the centrifugation gives qualitatively/quantitatively different products



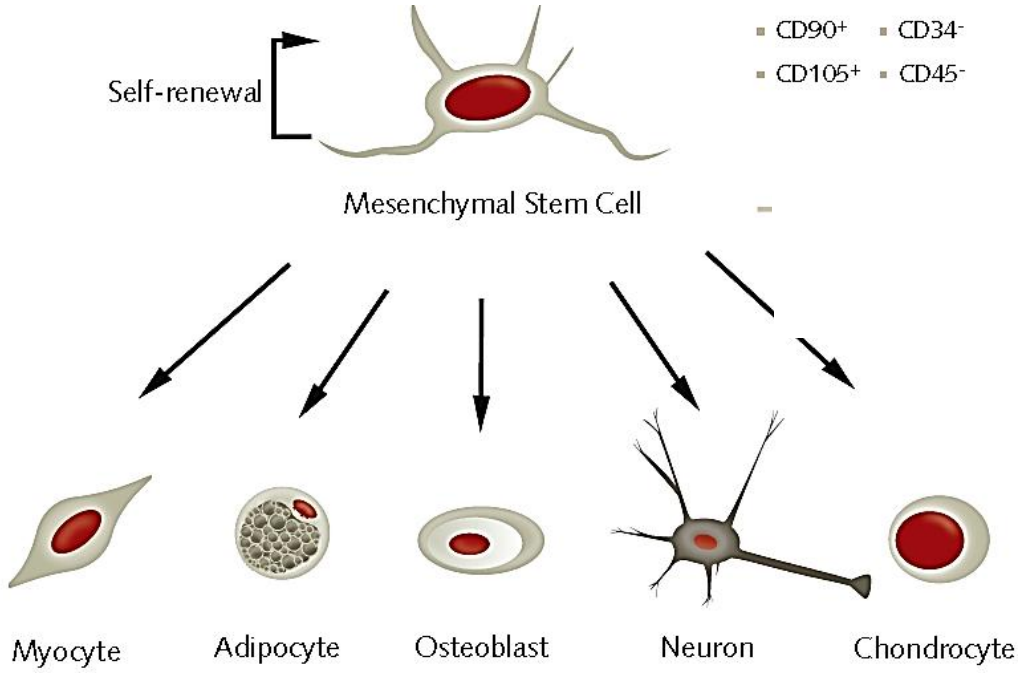


Relevance of BMAC

➢ **Mesenchymal Stem Cells (MSCs) =** Multipotent, stromal (connective tissue) stem cells hypothesized as the most promising cell for tissue regeneration and/or restoration

- Found in bone marrow, adipose tissue, amniotic fluid, endometrium, etc.
- Secrete cytokines and regulate tissues' microenvironments via immune receptors
- Can differentiate into mesodermal lineages (osteocytes, adipocytes, chondrocytes)

Mesenchymal Stem Cell



Relevance of BMAC

Limited evidence from animal and human studies

Apparent extrapolations from molecular biology led to hypothesizing that direct application of growth factors, stem cells, and/or progenitor cells to certain bone and joint pathologies

Might facilitate or expedite regeneration and/or restoration of tissue.

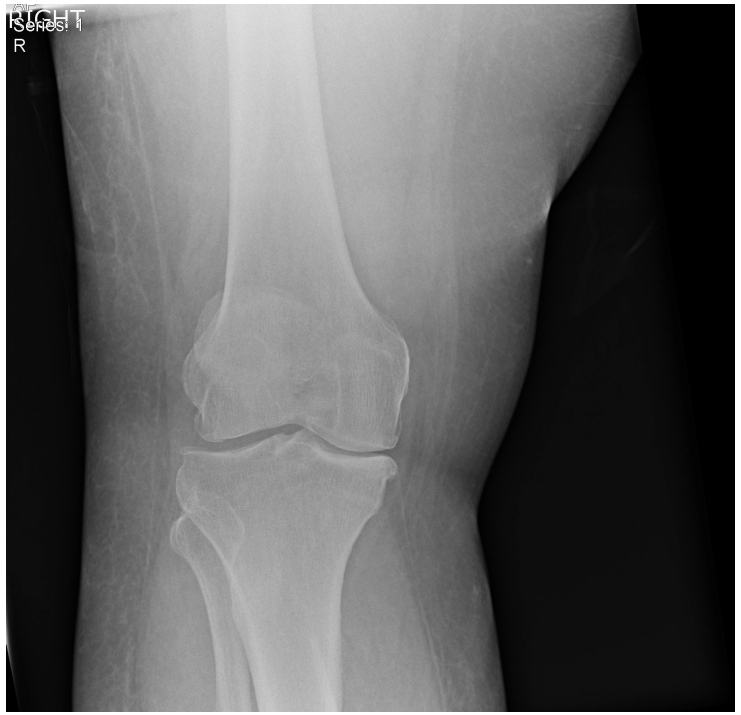
Patient Examples

- 52 year old Hispanic male
  - Referred for total knee replacement.
- PMH
  - Chronic Lumbago, Spinal DJD
  - Bilateral knee osteoarthritis
  - Bilateral LE lymphedema
- Morbid obesity with BMI of 50.5 and history of gastric bypass.

Patient 1

- Previous treatments (limited improvements)
  - physical therapy
  - cortisone injections
  - visco supplementation
  - Tylenol and opiate pain medications
- The patient ambulates with a cane
- Pain is impacting his mobility, ability to perform job functions and affecting sleep he rates his pain as a 10/10.

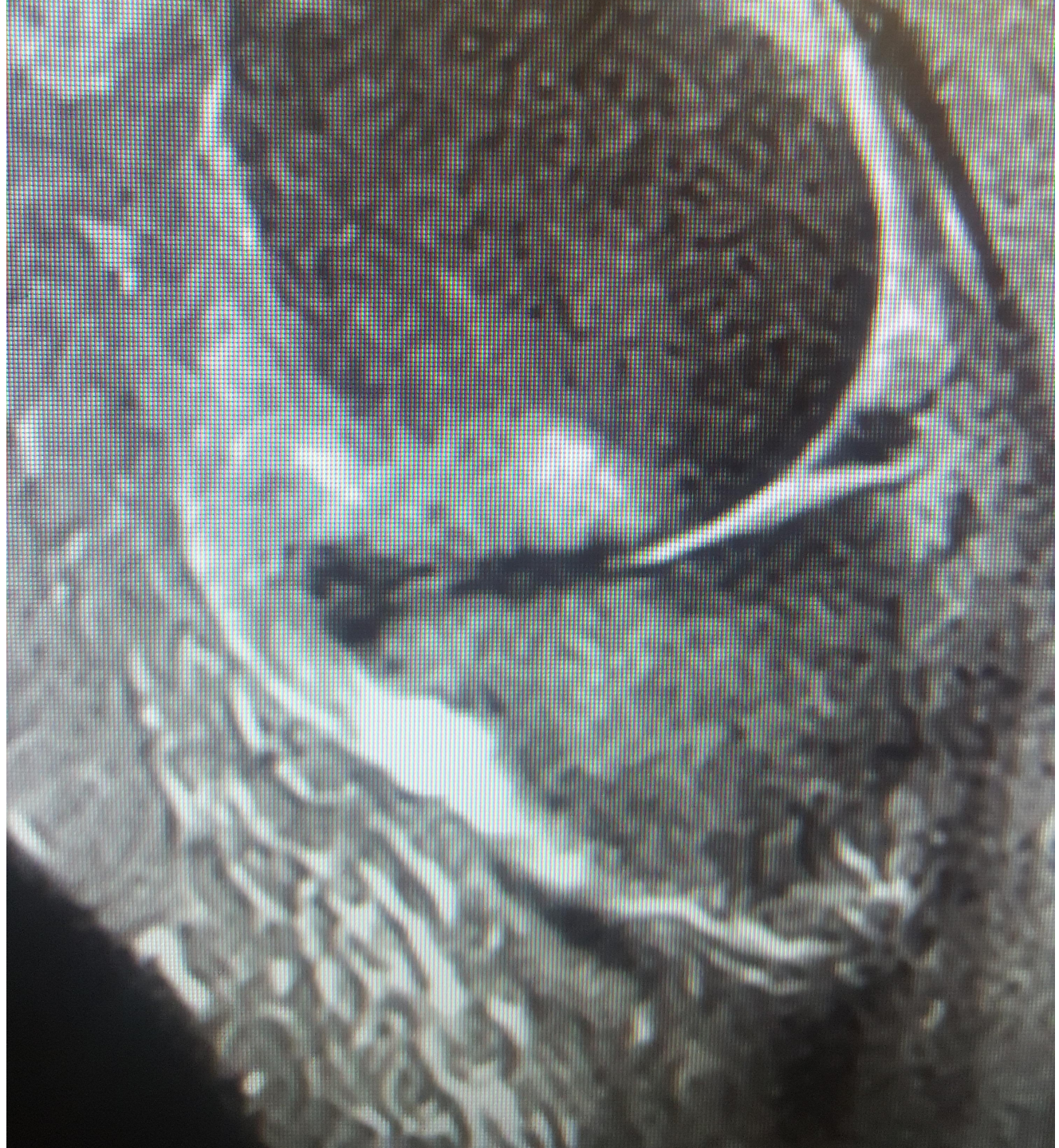
Xray: Right knee



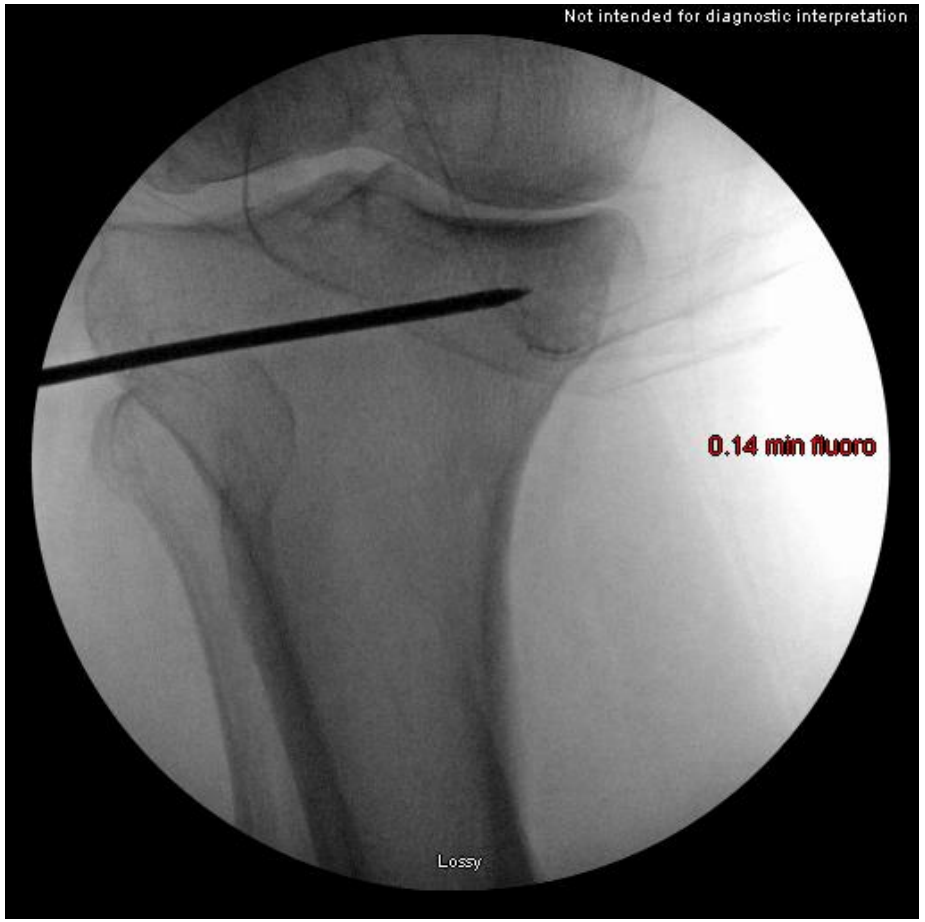
MRI Images

CONCLUSION:

1. Chronic complex posterior horn, body and anterior horn medial meniscus tear. The midbody extruded into the gutter.
2. Medial compartment arthropathy. Loss of joint space. Osteophytes. Intermediate to high grade chondromalacia. Marrow reaction weightbearing medial femoral condyle and tibia.
3. Patellofemoral arthropathy.
4. Capsulosynovitis.
5. Tibial collateral ligament bursitis.
6. Baker's cyst.
7. Please see above.



Intraoperative Images



Post Operatively

- 6 months post operatively he rates his overall pain as a 6 out of 10 and notes that majority of it is stemming from his back.
- He is back to working full time with no limitations and has noted improvements in his ADL's and is no longer utilizing a cane to ambulate.
- Patient is hopeful to continue to postpone TKA.
- The patient noted almost equivalent pain relief with the BMC on the right and the PPP on the left
- While this patient has a noted improvement in his pain and daily function he has not noticed any changes in his weight.

Patient Example

- 50 year old African American male
- Bilateral knee pain with the right being worse than the left
- Referred for evaluation for right knee TKA.
- PMH
  - DM II
  - Hypertension
  - Chronic Lumbago with DJD
  - Bilateral LE lymph edema
  - Morbid obesity with BMI of 60.5 and history of gastric bypass.
    - ICU for one month post bypass

Patient Example

- Previous treatments (limited improvements)
  - physical therapy
  - cortisone injections
  - visco supplementation
  - Tylenol and opiate pain medication all with.
- Patient ambulates with a rolling walker or a cane.
- The patient notes that he is unable to continue to work as a football coach
- considering dropping out of college as he has severe difficulty with getting to his classes. Rates his pain as a 10 out of 10 and states that he is ready for a TKA at this point.

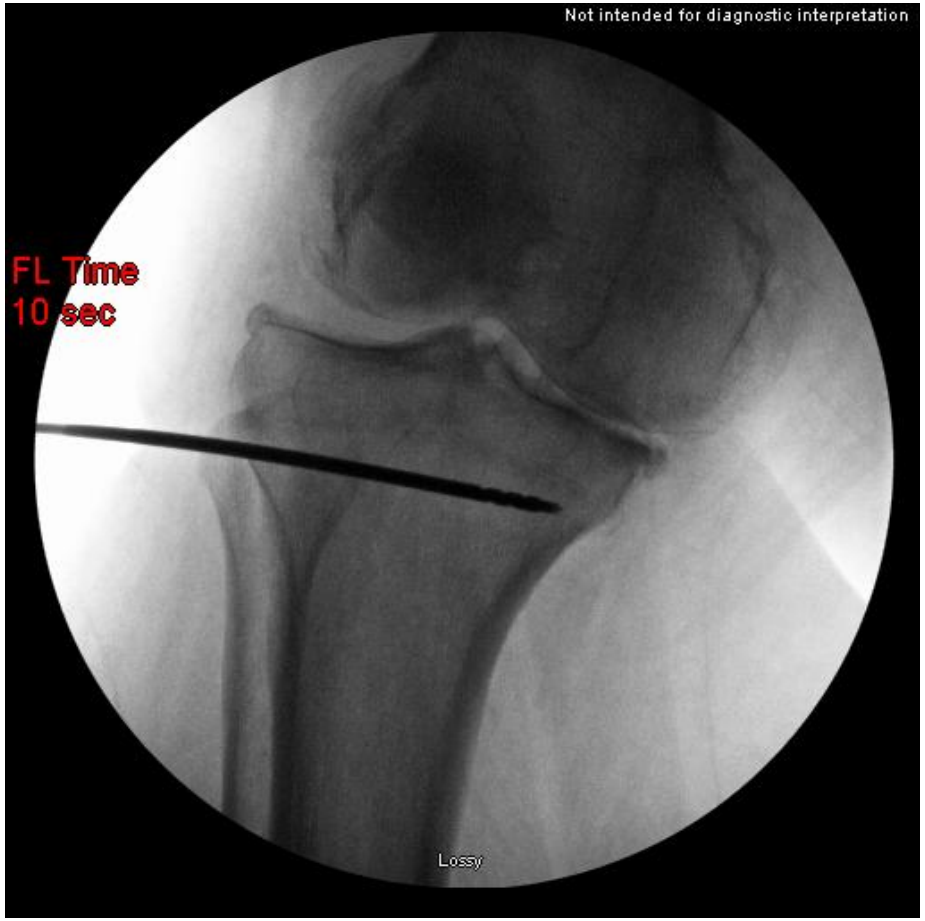
Xray: Right knee

MRI images

CONCLUSION:

1. Advanced medial compartment osteoarthritis with bone on bone complete joint space loss and moderate lateral tibial shift.
2. Medial meniscus is macerated and extruded peripherally.
3. Trace of joint effusion with several osseous intra-articular fragments.
4. Moderate patellofemoral and mild lateral compartment chondromalacia and osteoarthritic changes.
5. At least a partial chronic ACL tear is present. The ACL is thin in appearance and there is osseous hypertrophy of the lateral femoral condyle subjacent to the ACL origin.

Intraoperative Images



Post operatively

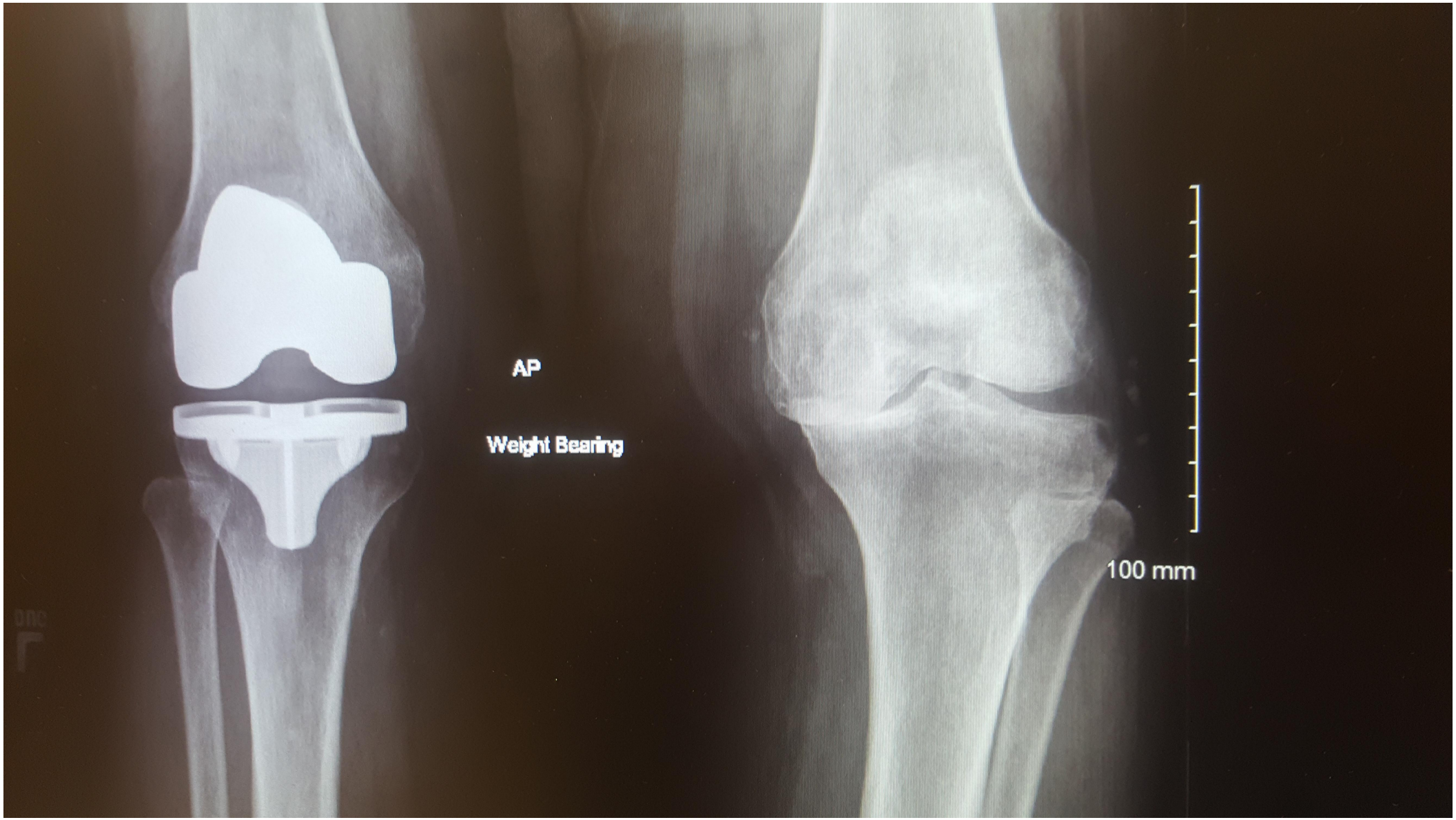
- 6 months post operatively
  - pain is a 0-2 out of 10
- He returned to full time coaching and is able to get out on the field and run drill with the kids instead of coaching from the bleachers.
- He was able to continue going to school and graduate due to the relief in his pain and increased mobility and function.
- He no longer uses a walker to ambulate, he will rarely use a cane only when walking on uneven surfaces.
- He has been able to return to the gym and has lost 60lbs in the process and notes that he will continue to put off his TKA.

Patient Example

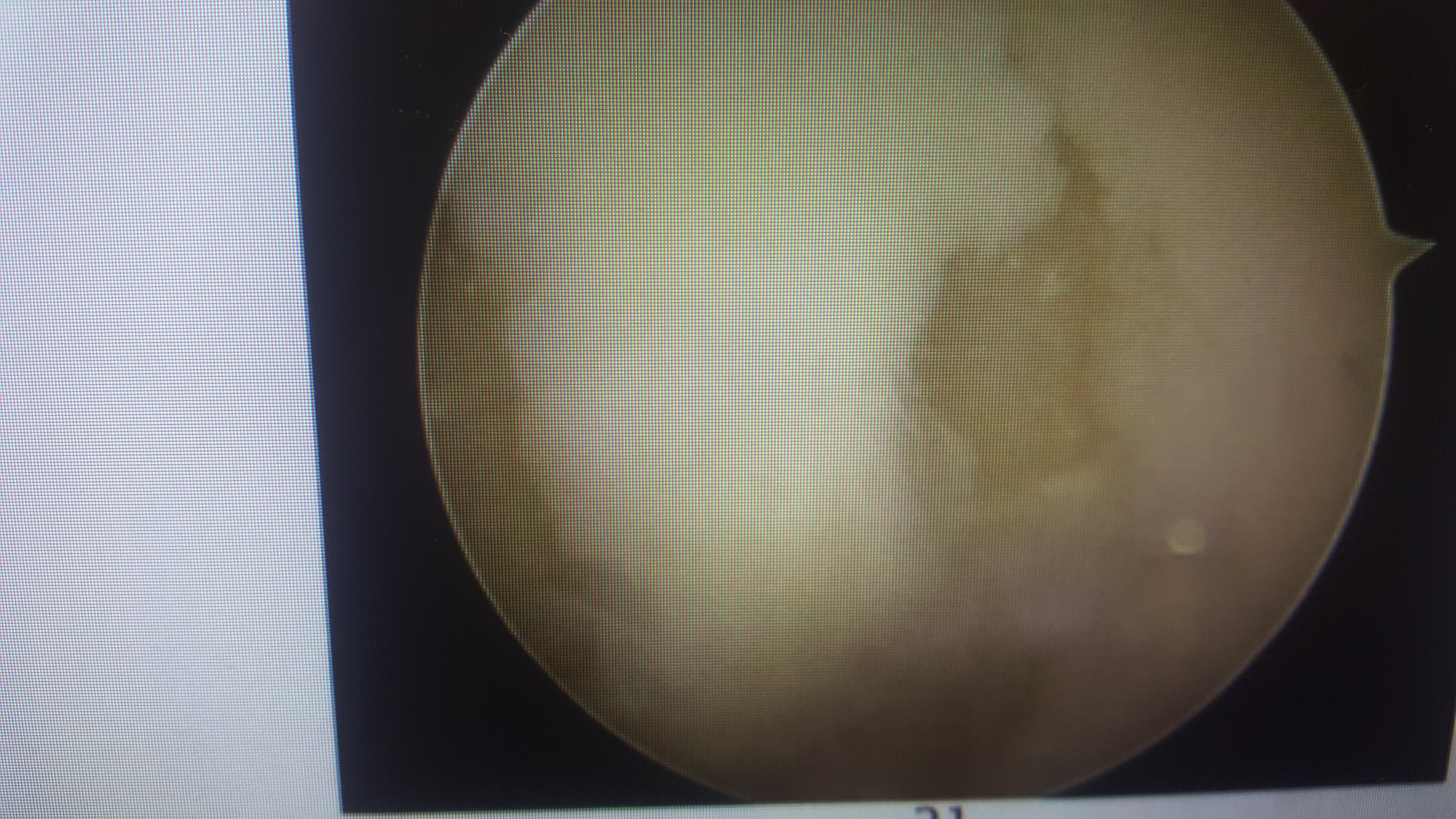
- 58 year old African American woman
  - Referral for consideration of left total knee arthroplasty
  - Already had right total knee arthroplasty

- PMH
  - Depressive disorder
  - HTN, Diabetes, lower extremity edema
  - Fatty liver 5/14
  - Hypertrophic obstructive cardiomyopathy
  - Opioid dependency
  - Tobacco use

  - BMI 35 with history of Gastric Bypass

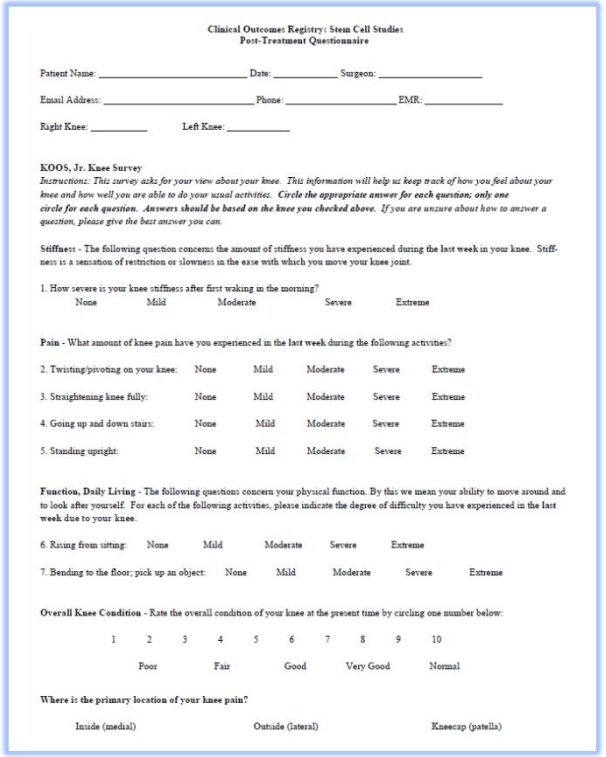

AP
Weight Bearing
100 mm


40 mm



Retrospective Study

- Scientific Methods
  - Retrospective review of all patients who underwent BMAC procedure
    - N=54
  - Patients completed validated questionnaires at three-month intervals
    - **KOOS Jr.**
    - **Overall knee condition**
    - Primary location of pain
    - Modified VR-12
    - **General Fitness**
    - Cincinnati Knee Rating - Symptom Rating Scale
    - Modified Lower Extremity Functional Scale (LEFS)
    - **Patient Expectations**
    - Work Status



Clinical Outcomes Registry: Stem Cell Studies
Post-Treatment Questionnaire

Patient Name: _____ Date: _____ Surgeon: _____

Email Address: _____ Phone: _____ EMR: _____

Right Knee: _____ Left Knee: _____

KOOS, Jr. Knee Survey
Instructions: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to do your usual activities. Circle the appropriate answer for each question; only one circle for each question. Answers should be based on the knee you checked above. If you are unsure about how to answer a question, please give the best answer you can.

Stiffness - The following question concerns the amount of stiffness you have experienced during the last week in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

1. How severe is your knee stiffness after first waking in the morning?
None Mild Moderate Severe Extreme

Pain - What amount of knee pain have you experienced in the last week during the following activities?

2. Twisting/pivoting on your knee: None Mild Moderate Severe Extreme
3. Straightening knee fully: None Mild Moderate Severe Extreme
4. Going up and down stairs: None Mild Moderate Severe Extreme
5. Standing upright: None Mild Moderate Severe Extreme

Function, Daily Living - The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty you have experienced in the last week due to your knee.

6. Rising from sitting: None Mild Moderate Severe Extreme
7. Bending to the floor; pick up an object: None Mild Moderate Severe Extreme

Overall Knee Condition - Rate the overall condition of your knee at the present time by circling one number below:

1 2 3 4 5 6 7 8 9 10

Poor Fair Good Very Good Normal

Where is the primary location of your knee pain?

Inside (medial) Outside (lateral) Kneecap (patella)

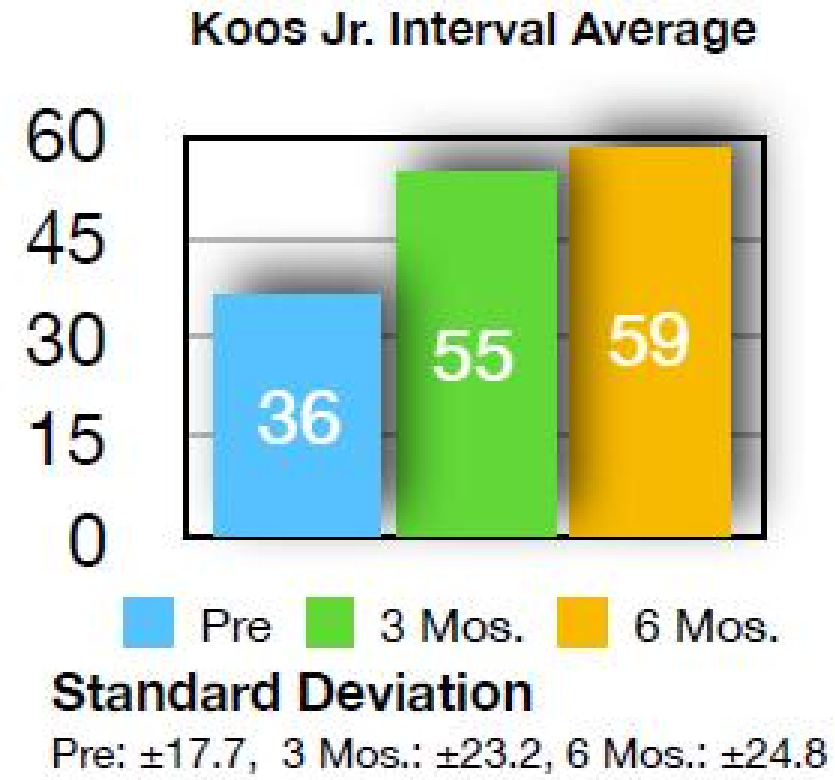
Retrospective Study

- Patient Demographics:
  - Males: 15
  - Females: 39
  - Average Age: 57 (range 36-76)
  - Average BMI: 38.91 kg/m^2 (range 19.77 – 56.95)

Preliminary Results: Patient Follow-Up

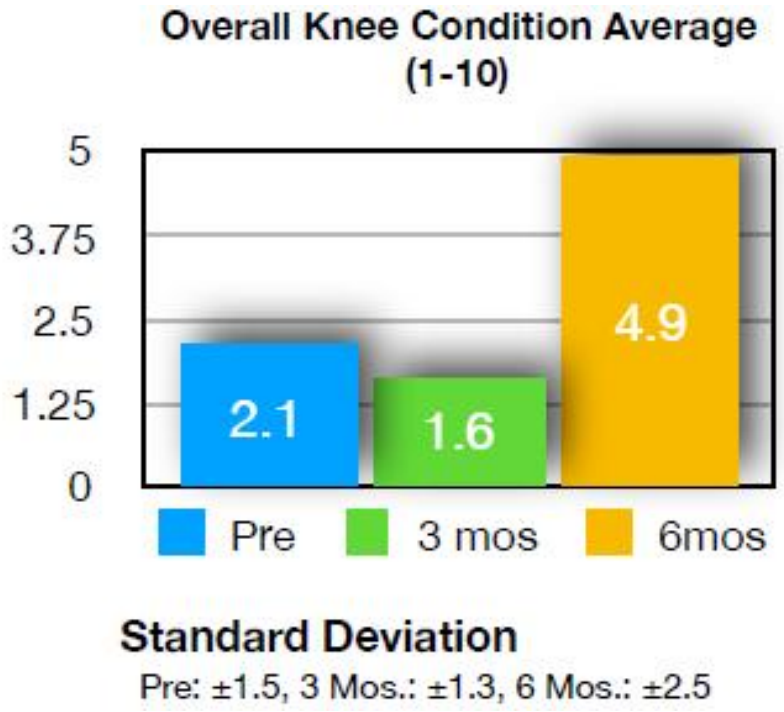
- Goal = 90% follow-up at each time point
  - Pre: N = 54 (53/54 = 98% follow-up)
  - 3 Months: N = 36 (36/38 = 95% follow-up)
  - 6 Months: N = 43 (43/49 = 88% follow-up)
  - 9 and 12 Months: Currently collecting data

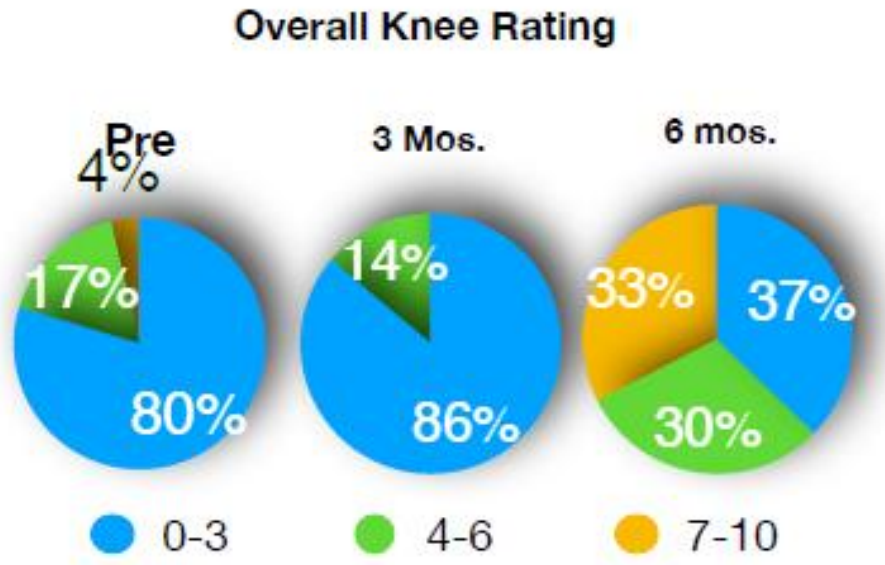
Preliminary Results: KOOS Jr.



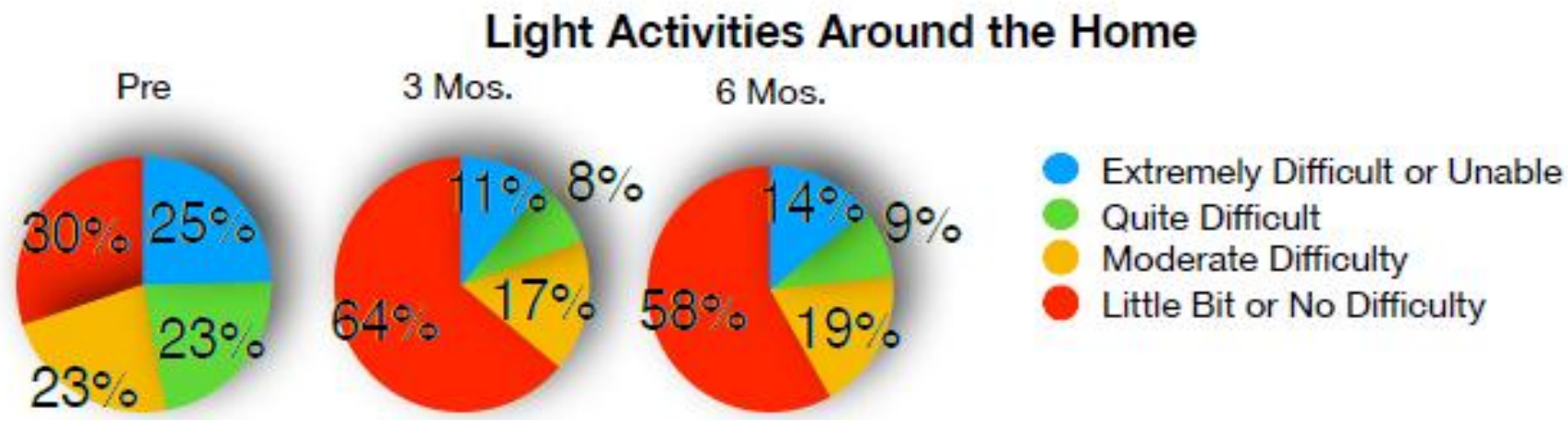
Preliminary Results: Overall Knee Rating

- Rated knee on a scale of 1-10
  - 1 = Poor
  - 10 = Normal



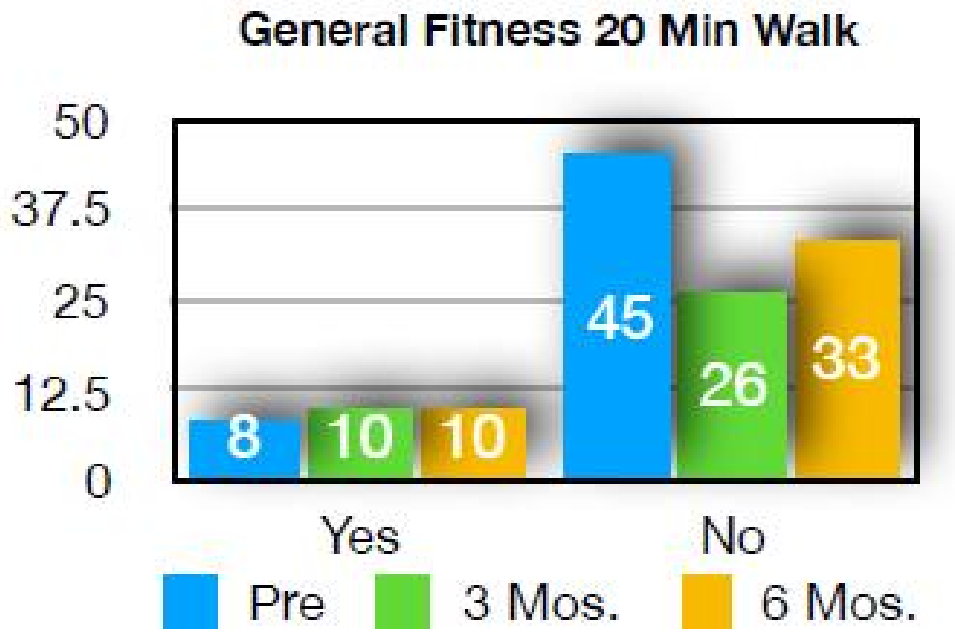


Preliminary Results: Light Activities



Preliminary Results: General Fitness

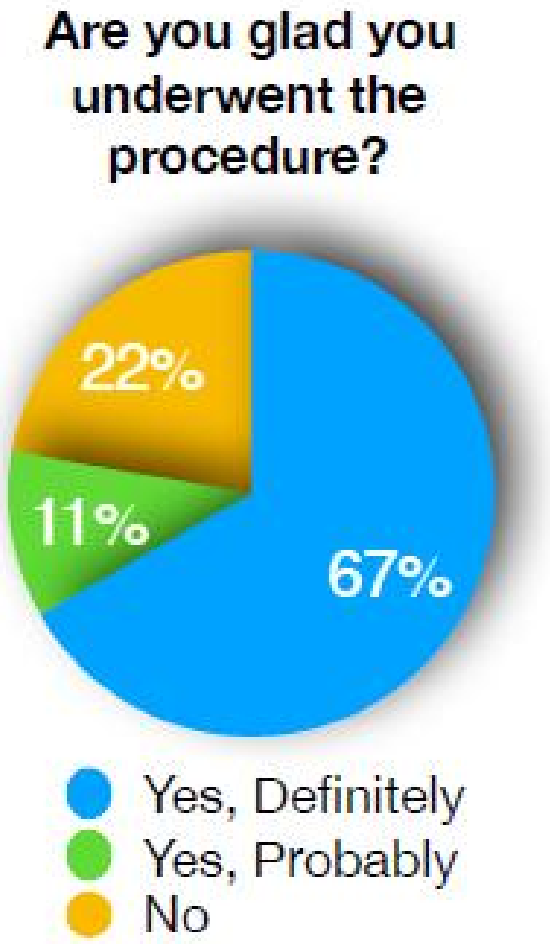
- Some increase in general fitness, but minimal
- Patients reported improvements in overall condition and KOOS, Jr
  - Does not correlate with increased general fitness



Preliminary Results: Patient Satisfaction

- Most patients were glad that they underwent the procedure.

- At 6-months, the BMAC procedure showed promising results with improvement in the KOOS Jr. score, overall knee rating score and ability to do light activities around the house.



Relevance of BMAC to Musculoskeletal Science

- BMAC is one of only several FDA-approved means to deliver stem cells and growth factors
- Despite MSCs comprising only ≤ 0.01% of BMAC mononuclear cells, high concentration of growth factors in BMAC implies potential anabolic and anti-inflammatory effects
- Examples of hypothesized clinical indications for BMAC previously studied:
  - **Osteoarthritis**
  - Osteochondral defects/lesions
  - Fracture healing
  - Lumbar arthrodesis
  - Discogenic pain
  - Osteonecrosis
  - Bony defects
  - Rotator cuff pathology
  - ACL injuries
  - Tennis elbow
  - Achilles tendon rupture

Adipose derived stem cells

- Yokoto 2019, American Journal of Sports Medicine
- 80 patients with intraarticular injection
  - Retrospective review
  - 42 ASC (adipose derived stem cells) cultured 12.5 million cells
    - Greater early response
  - 38 SVF (stromal vascular fraction) aspirated noncultured

- VAS pain
  - 77 → 58 KL 2
  - 43 → 38 KL 4

Current Evidence for BMAC Treatment of Osteoarthritis

BMAC treatment for osteoarthritis appears to be safe

BMAC's rapid increase in use over other sources of stem cells, cytokines and growth factors for treatment of osteoarthritis

BMAC is one of only several FDA-approved means to deliver stem cells (minimally manipulated)

Clinical studies addressing BMAC for osteoarthritis overall indicate good results

However, diversity in chosen outcome measures by authors prevents evidence-based comparisons between studies

Despite prevalence of use of BMAC for osteoarthritis internationally, there are insufficient level 1 or 2 evidence studies to support its use

Sufficiently powered RCT's with gold standard outcome measures and well-defined end points are necessary to confirm efficacy of BMAC for osteoarthritis in addition to aspirate volume and concentration, safety, duration of clinical benefit, need for scaffold, etc.

Thank You!