Regenerative Medicine in Primary Care

PRP, cell-based therapies, and what to say to patients

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Your patients are already asking about this

~14 million

US adults with symptomatic knee osteoarthritis

2,754

US clinics marketing unlicensed stem cell treatments in 2021

$500–$2,500

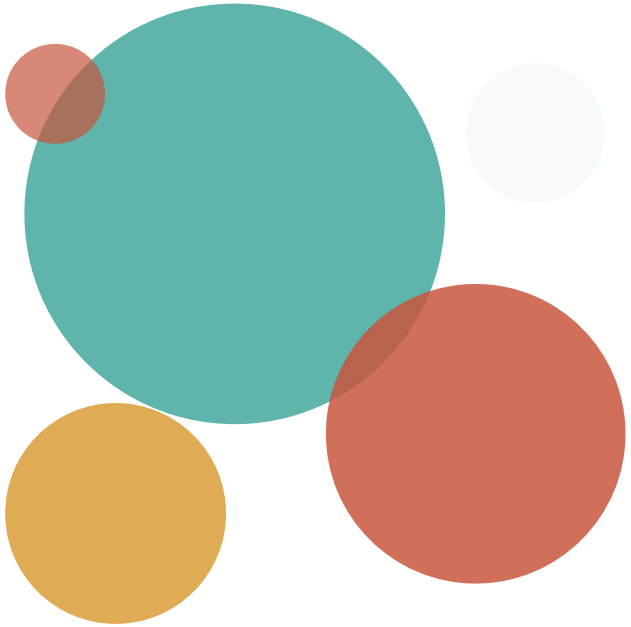
Typical self-pay price per PRP injection; cell-based procedures cost more

Sources: Deshpande, Arthritis Care Res 2016; Turner, Cell Stem Cell 2021.

When patients hear about these treatments from ads, seminars, or friends, their PCP is often the first clinician they ask.

Today's objectives

- Define stem cells and explain how PRP and cell-based therapies work
- Interpret the evidence by condition, including where guidelines disagree
- Identify good referral candidates and what to include with the referral
- Recognize regulatory red flags and steer patients away from unsafe products



The bottom line, up front

PRP

A reasonable option for selected patients

Mild to moderate knee OA and some chronic tendinopathies, after at least 3 months of good conservative care. Usually self-pay.

CELL-BASED THERAPY

Promising, but not proven

In the largest randomized trial, bone marrow, fat, and cord-derived cells were no better than a steroid injection. Clinical trials are the best route.

UNAPPROVED PRODUCTS

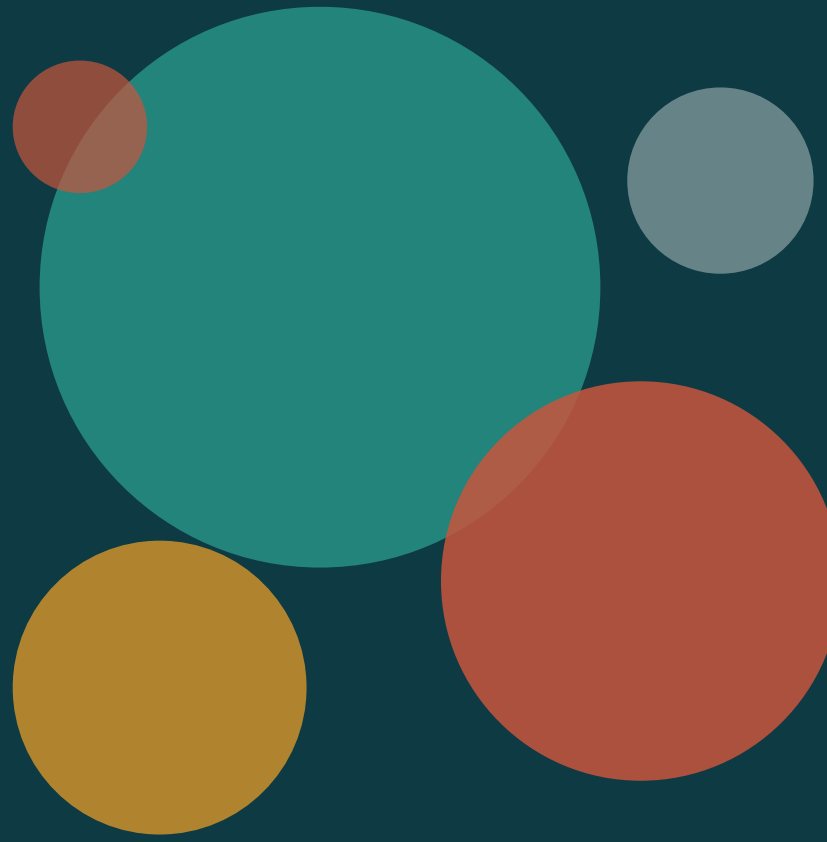
Early, proceed with caution

Amniotic, cord blood, and exosome products, and IV or spinal "stem cell" infusions, are largely unapproved and have caused real harm.

01

Foundations

What regenerative medicine is and where it fits



Regenerative medicine runs from routine to unproven

PRP

Concentrated platelets from the patient's own blood. Widely available; evidence varies by condition.

Bone marrow & fat

Same-day concentrates of the patient's own tissue (BMAC, microfragmented fat). Small, mixed evidence.

Lab-grown MSCs

Culture-expanded cells. Investigational in the US; legally available only in trials.

Donor & exosome products

Amniotic, cord, and exosome products. Mostly unapproved; linked to serious harms.

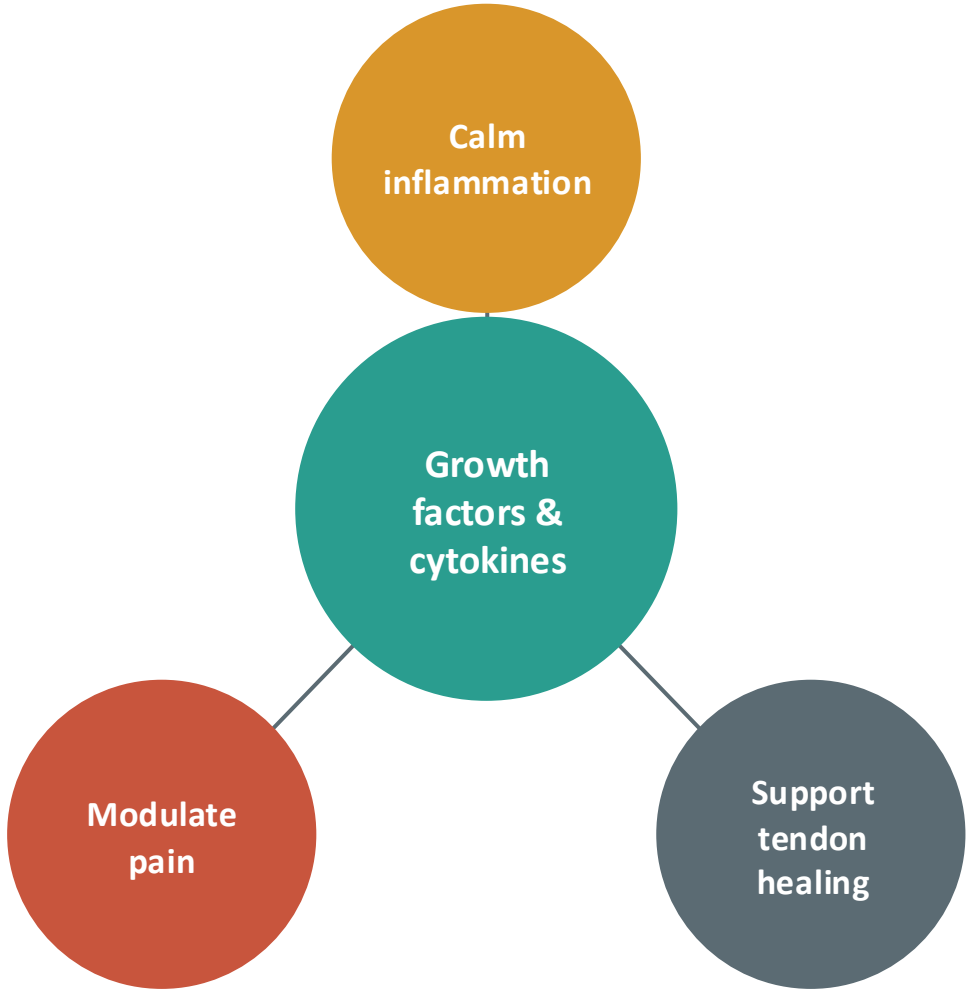


More evidence, clearer regulation

Less evidence, more regulatory risk

These treatments send signals; they don't rebuild tissue

- **Platelets:** Release growth factors (PDGF, TGF-β, VEGF, IGF-1) that influence healing and inflammation.
- **Cells:** Injected MSCs mostly act by paracrine signaling. Few survive or turn into new tissue.
- **Effects:** Mainly on pain, inflammation, and tendon healing.
- **Not shown:** Convincing cartilage regrowth in human OA trials.



Orthobiologics come after conservative care, not instead of it

1

Foundation

Education, weight loss, exercise

2

Conservative

PT, topical or oral NSAIDs, bracing

3

Standard injections

Corticosteroid or hyaluronic acid

Referral point

4

Orthobiologics

PRP for selected patients

5

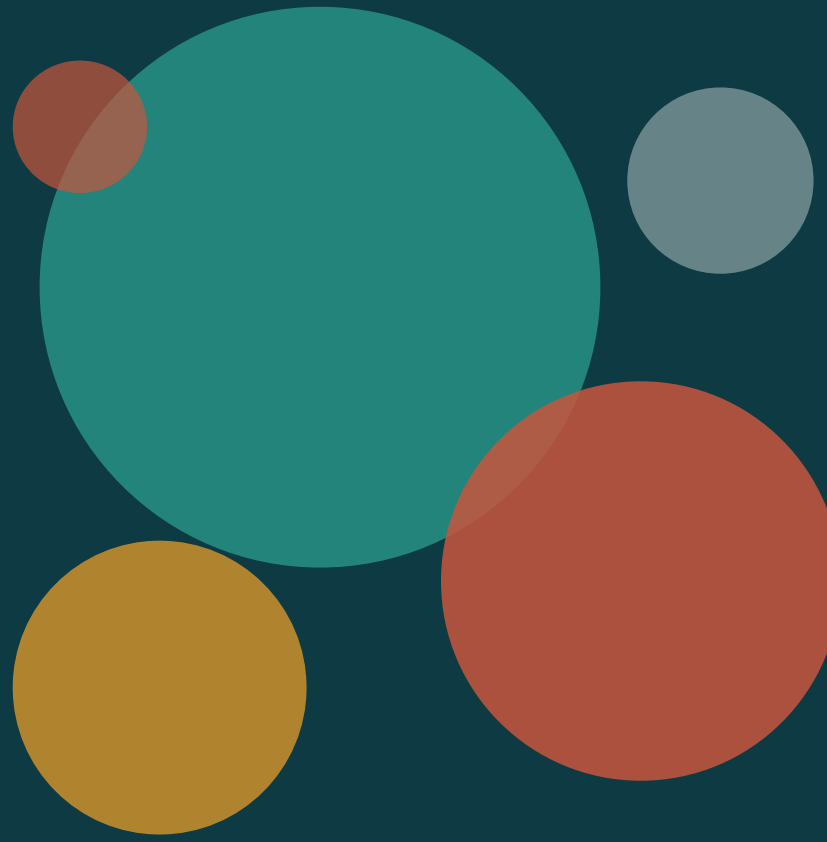
Surgery

Arthroplasty or repair evaluation

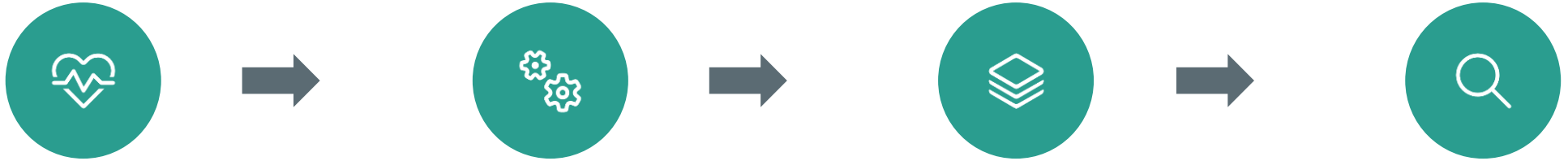
02

Platelet-rich plasma

What it is, where it works, and who benefits



PRP concentrates platelets from the patient's own blood



Draw

15–60 mL of venous blood

Spin

Centrifuge separates platelets from red cells

Concentrate

Platelets at about 2–8× baseline or target dose

Inject

Ultrasound-guided, same visit

Leukocyte-poor PRP

Usually preferred for joints such as the knee; fewer inflammatory white cells.

Leukocyte-rich PRP

Often used for chronic tendinopathy, such as lateral elbow and gluteal tendons.

There is no standard recipe: commercial kits vary widely in platelet dose and cell content, which makes studies hard to compare.

Knee OA has the strongest PRP data, but guidelines disagree

Pooled trials

Meta-analyses favor PRP over hyaluronic acid and saline for pain and function at 6–12 months, mostly in mild to moderate OA.

Berrigan et al. (Arthroscopy, 2025): reviewed 31 knee OA trials. The 28 positive trials used a mean of about **5.5 billion platelets**, and the 3 negative ones about 2.3 billion. Meta-regression showed bigger improvements at higher doses at both 6 and 12 months.

Bansal et al. (Scientific Reports, 2021): randomized 150 patients to about **10 billion platelets in 8 mL** or hyaluronic acid. The PRP group used less rescue medication at 1 year and had lower inflammatory markers (IL-6, TNF-α).

Patel et al. (Orthopaedic Journal of Sports Medicine, 2024): a triple-blind head-to-head trial of 99 knees. **About 5.7 billion platelets outperformed about 2.8 billion at 6 months**: WOMAC pain fell 54% versus 28%, and 96% versus 68% of patients were satisfied.

What the guidelines say

Against

ACR 2026: Strong recommendation against PRP for knee and hip OA, **citing nonstandard preparations**.

Limited

AAOS 2021: PRP may reduce pain and improve function; limited strength of evidence.

Consider

AAPM&R 2026: Consider for mild to moderate (KL 1–3) OA that persists despite conservative care.

Takeaway: offer PRP through shared decision-making, not as a standard of care.

For tendons, results depend on the tendon

Evidence supports	Mixed or limited	Not effective
Lateral elbow tendinopathy Outperforms steroid beyond 3–6 months	**Patellar tendinopathy** Small trials with inconsistent results	**Chronic Achilles tendinopathy** No better than sham (ATM trial, JAMA 2021)
Plantar fasciopathy Similar to or better than steroid at longer follow-up	**Gluteal tendinopathy** One positive RCT against steroid	**Acute Achilles rupture** No functional benefit (PATH-2, BMJ 2019)
Rotator cuff repair (add-on) May lower retear rates after surgery	**Hip OA** Few trials; benefit unclear	**Acute hamstring strain** No faster return to play (NEJM 2014)

How the knee OA injection options compare

Option	Onset	How long it lasts	Cost and coverage	Watch for
Corticosteroid	Days	About 4–8 weeks	Low; usually covered	Hyperglycemia; cartilage loss with repeated use
Hyaluronic acid	2–4 weeks	Up to about 6 months	Moderate; coverage varies	Small benefit over saline
PRP	4–8 weeks	6–12 months in responders	$500–$2,500 per injection; self-pay	Pain flare for 2–5 days
Cell-based (BMAC, adipose)	4–8 weeks	No better than steroid at 12 months	$3,000–$10,000+; self-pay	Harvest-site pain; product variability

Typical ranges; local prices and payer policies vary. Cell-based row reflects the MILES trial (Mautner, Nat Med 2023).

Repeated steroid injections carry a structural cost

2×

more cartilage volume loss over 2 years

Triamcinolone every 3 months vs. saline: 0.21 mm vs. 0.10 mm of cartilage loss, with no difference in pain.

McAlindon et al., JAMA 2017

What this means in practice

- Steroid is still a useful short-term tool, especially for flares.
- If a patient needs injections every few months, discuss alternatives.
- This tradeoff is one reason patients and PCPs consider PRP.

Good PRP candidates have mild to moderate disease

More likely to benefit

- KL grade 1–3 knee OA
- Tendinopathy of 3+ months despite a structured loading program
- Short-lived steroid relief, or steroid best avoided (e.g., poorly controlled diabetes)
- **Wants to stay active or delay surgery**
- Accepts the cost and a modest, uncertain benefit

Less likely to benefit

- KL grade 4 (bone-on-bone): refer for arthroplasty consult
- Locking, catching, or instability: refer to orthopedics
- Active inflammatory arthritis, gout, or septic joint
- Expects cartilage regrowth or a cure
- Can't pause NSAIDs or tolerate a post-injection flare

Screen for these before you refer

CONTRAINDICATION

Infection

Local or systemic infection: defer until it resolves.

CONTRAINDICATION

Malignancy

Active cancer at or near the site, or a hematologic malignancy.

CONTRAINDICATION

Low platelets

Thrombocytopenia or platelet dysfunction. Check a CBC if unsure.

PRECAUTION

Anticoagulants

Coordinate with the prescriber; don't stop them without a plan.

PRECAUTION

NSAIDs

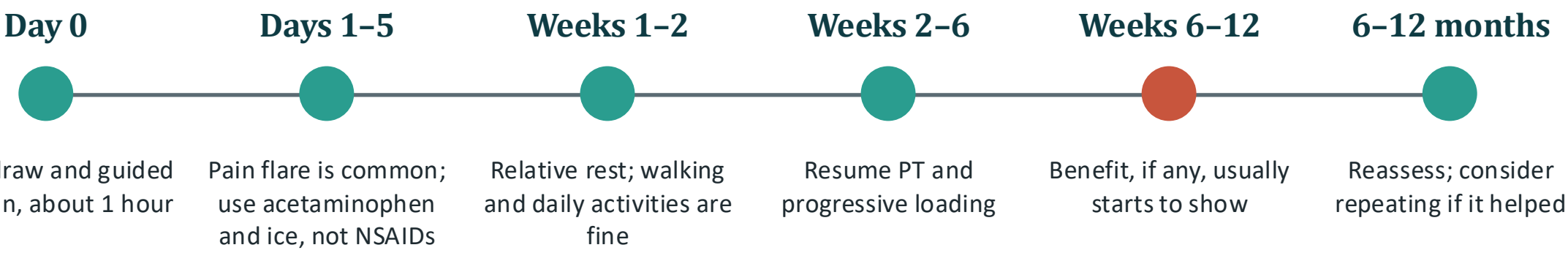
Often held about 1 week before and 2 weeks after; protocols vary.

PRECAUTION

Recent steroid

Many protocols wait 4–6 weeks after a steroid injection at the site.

What your patient can expect after PRP



Most protocols use 1–3 injections spaced 2–6 weeks apart. Tell patients to expect gradual change, not overnight relief.

PRP is usually self-pay, so set expectations early

$500–$2,500

Typical price per injection; a series may need 1–3

0232T

Category III CPT code; most payers deny it as investigational

NCD 270.3

Medicare covers PRP only for chronic non-healing wounds, not joints or tendons

TRY SAYING

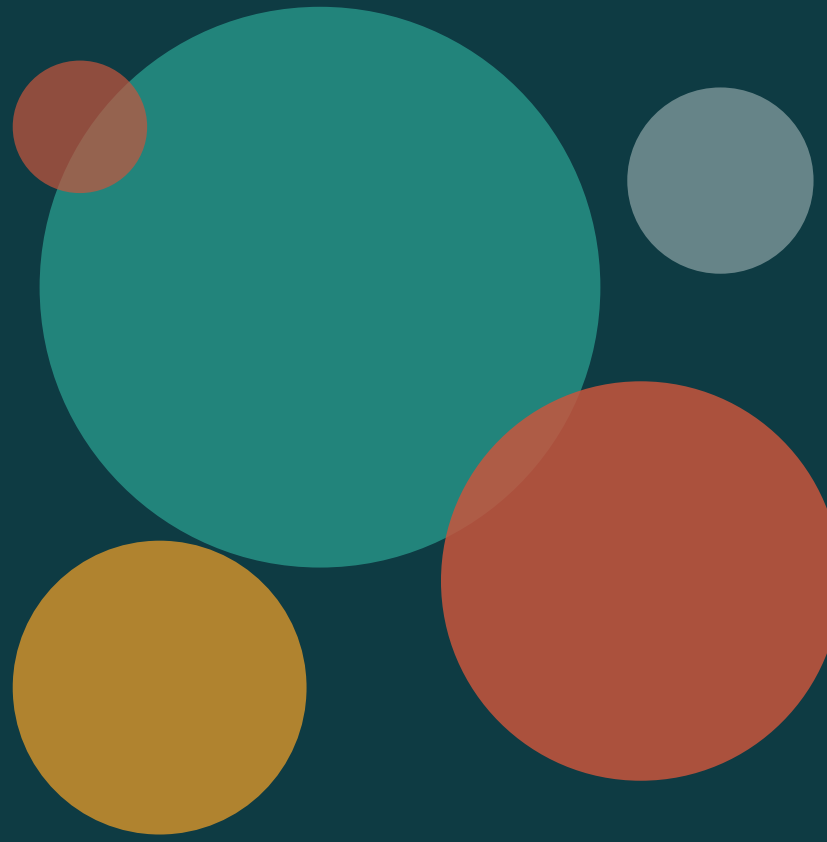
"PRP may help, but it isn't guaranteed, and insurance usually won't pay. Let's make sure it's worth it for you."

HSA and FSA funds can often be used.

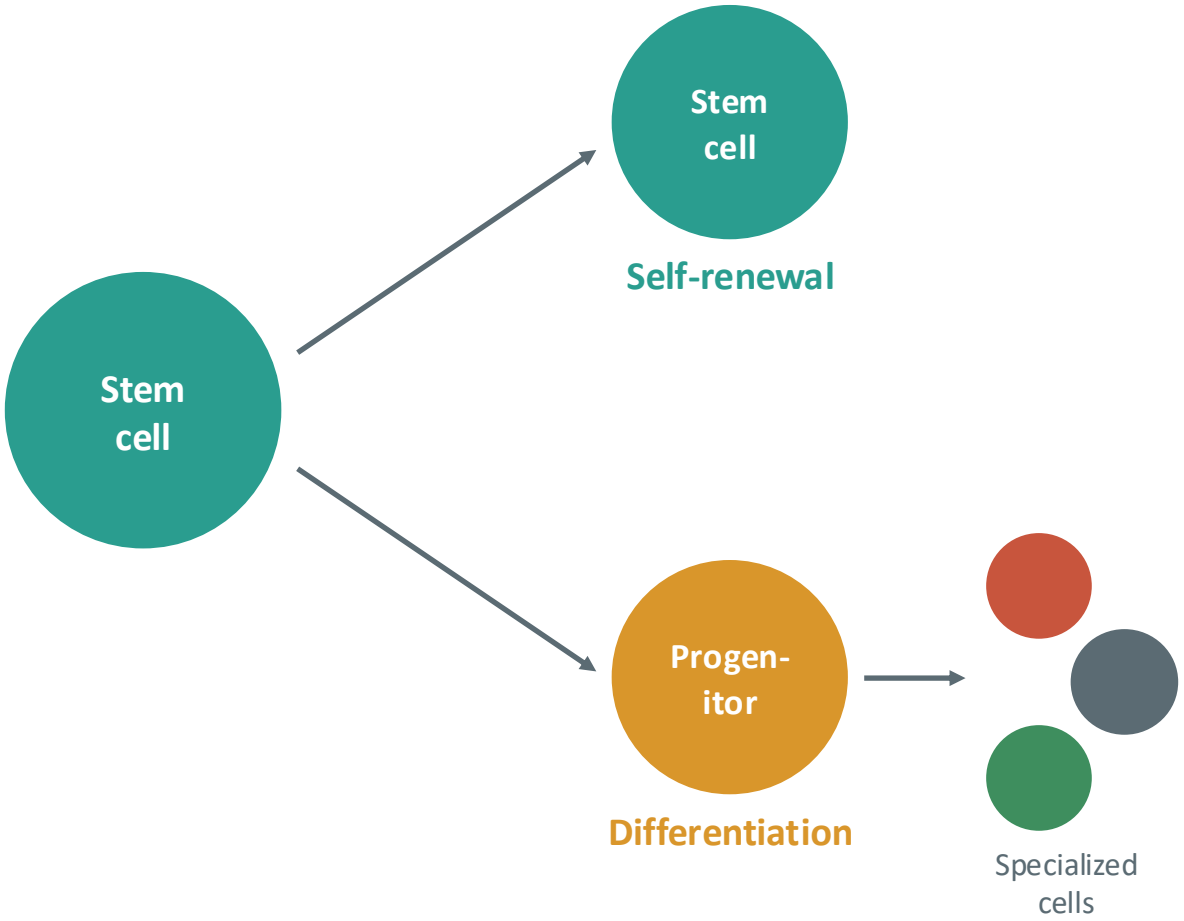
03

Cell-based therapies

What stem cells are, how they work, and what the evidence shows



Two properties define a stem cell



Self-renewal

Divides to make copies of itself over long periods, so the stem cell pool lasts.

Potency

Can differentiate into one or more specialized cell types.

A true stem cell has both. Most cells in a "stem cell" injection have neither in meaningful numbers.

Stem cells are classified by how many cell types they can become

Totipotent
Every cell type, including the placenta

Fertilized egg and the earliest embryo cells

Pluripotent
Any cell in the body, but not the placenta

Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs)

Multipotent
Several cell types within one family

Blood-forming stem cells (HSCs); mesenchymal stromal cells (MSCs)

Unipotent
A single cell type

Muscle satellite cells; sperm-producing stem cells



The main types of stem cells and what they do

TYPE	SOURCE	WHAT THEY DO	CLINICAL USE
Embryonic (ESCs)	Early embryos (blastocyst)	Pluripotent; can form tumors (teratomas)	Research, early trials
Induced pluripotent (iPSCs)	Adult cells reprogrammed in the lab (2006)	Pluripotent without embryos; disease modeling	Research, early trials
Hematopoietic (HSCs)	Bone marrow, blood, cord blood	Make all blood and immune cells	Standard of care
Mesenchymal stromal (MSCs)	Marrow, fat, umbilical cord, other tissues	Support tissue; signal to immune and repair cells	Approved: GVHD only
Tissue-resident	Muscle, skin, gut, cornea, and others	Maintain and repair their home tissue	Limited (skin, eye)

Most MSCs are "stromal," not proven "stem" cells

Lab definition of an MSC

ISCT minimal criteria, 2006

1. **Adherence:** sticks to plastic in standard culture
2. **Surface markers:** positive for CD73, CD90, and CD105; negative for CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR
3. **Differentiation:** can form bone, fat, and cartilage cells in a dish

Why the name matters

- **ISCT (2019):** use "mesenchymal stromal cells" unless stemness is shown in the body.
- **Caplan (2017):** proposed "medicinal signaling cells," reflecting how they work.
- Passing lab tests in a dish doesn't show they'll build tissue in a patient.

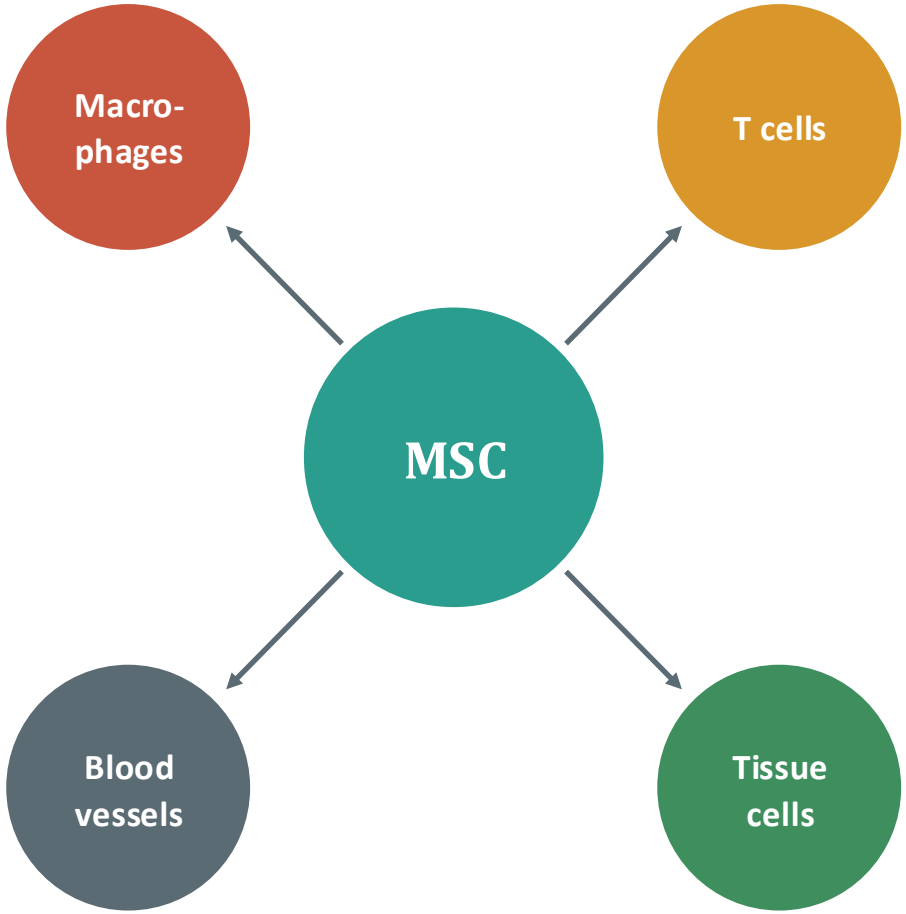
MSCs act mainly through paracrine signaling

Paracrine: a cell releases signals that act on nearby cells. (Endocrine signals travel through blood; autocrine signals act on the cell itself.)

Soluble factors
Growth factors and cytokines: VEGF, HGF, IGF-1, TGF-β, IL-10, PGE2, TSG-6

Extracellular vesicles
Exosomes carrying microRNA, proteins, and lipids to target cells

Direct contact
Cell-to-cell signaling and transfer of mitochondria to injured cells



Paracrine signals produce four main effects

Immunomodulation

Shift macrophages from inflammatory (M1) to repair (M2) states; dampen T-cell activation; expand regulatory T cells.

Key mediators: PGE2, IDO, TGF-β

Anti-inflammatory

Lower inflammatory cytokines such as IL-1β and TNF-α in the surrounding tissue.

Key mediators: TSG-6, IL-1Ra, IL-10

Trophic and angiogenic

Support survival of nearby cells and the growth of new blood vessels.

Key mediators: VEGF, HGF, IGF-1, FGF-2

Anti-fibrotic and protective

Limit scarring and reduce cell death in injured tissue.

Key mediators: HGF, exosomal microRNAs

MSCs need "licensing": inflammatory signals such as IFN-γ and TNF-α switch on their immune-calming program. Their effects depend on the tissue they land in.

What paracrine action means for patients

Effects are temporary: Most injected cells are cleared within days to weeks, so any benefit is likely to fade.

No new cartilage: Signaling can ease pain and inflammation, but that is not evidence of tissue regrowth.

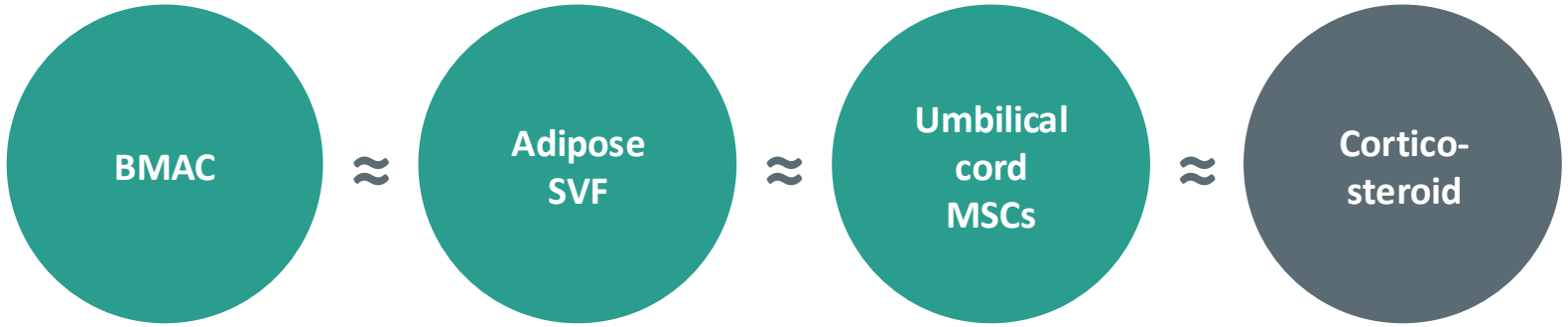
Products aren't interchangeable: Donor age, tissue source, dose, and processing all change what cells secrete.

"Cell-free" is not proven: Exosome and secretome products borrow this science but remain unapproved.

Common “stem-cell” products

BMAC	Bone marrow aspirate concentrate from the iliac crest; MSCs are ~0.001–0.01% of cells	Same-day, autologous
Microfragmented fat	Fat processed mechanically and reinjected the same day	Minimally manipulated
Stromal vascular fraction	Fat digested with enzymes to release cells	Unapproved drug
Culture-expanded MSCs	Cells grown in a lab for weeks before injection	Clinical trials only
Amniotic & cord products	Donor birth tissue; many contain no living cells	Mostly unapproved
Exosomes	Cell-derived vesicles marketed for many conditions	None approved

In the largest RCT, “cell injections did no better than steroid”



All four groups improved by about 35%. At 12 months, no cell product beat a corticosteroid injection for pain (VAS) or function (KOOS).

No saline control group

No procedure-related serious adverse events were reported.

Mautner et al., Nature Medicine 2023 (MILES trial)

480

patients with knee OA

4

randomized treatment arms

0

cell products superior to steroid

The list of FDA-approved cell therapies is short

Since 2011

Cord blood (HPC) products

Restore blood-forming function in blood cancers and inherited blood disorders

2016

MACI

Lab-grown autologous chondrocytes, surgically implanted for focal knee cartilage defects

2024

Ryoncil (remestemcel-L)

First approved MSC therapy: steroid-refractory acute GVHD in children

No FDA-approved stem cell product exists for osteoarthritis, back pain, neuropathy, or "anti-aging."

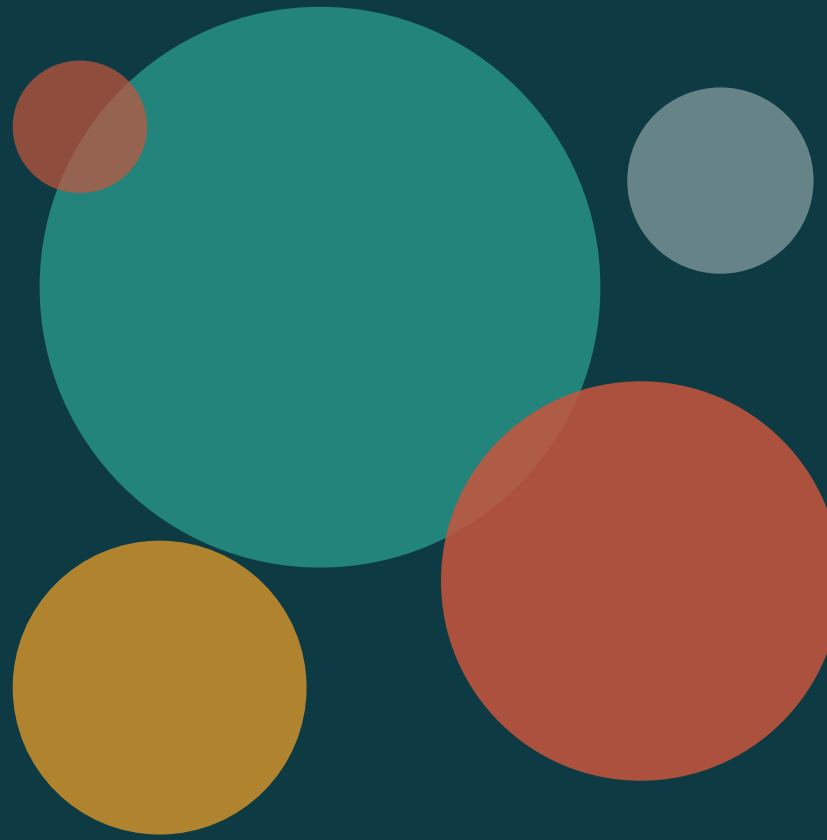
When cell-based care makes sense, refer to the right setting

Interested in cell therapy for OA	Consider referral to trusted partner. Can also consider an IRB-approved clinical trial.
Young, active patient with a focal cartilage defect	Orthopedic surgery for MACI, osteochondral grafts, or other cartilage repair.
Advanced, symptomatic OA (KL 4)	Orthopedic arthroplasty evaluation; orthobiologics are unlikely to help.

04

Regulation and red flags

Helping patients avoid unproven and unsafe products



FDA rules depend on how tissue is processed and used

Section 361 tissue product

No FDA premarket approval needed if ALL apply:

- Minimally manipulated
- Homologous use (same basic function)
- Not combined with another drug or device (limited exceptions)
- No systemic effect, or autologous or close-family use

Section 351 biologic (a drug)

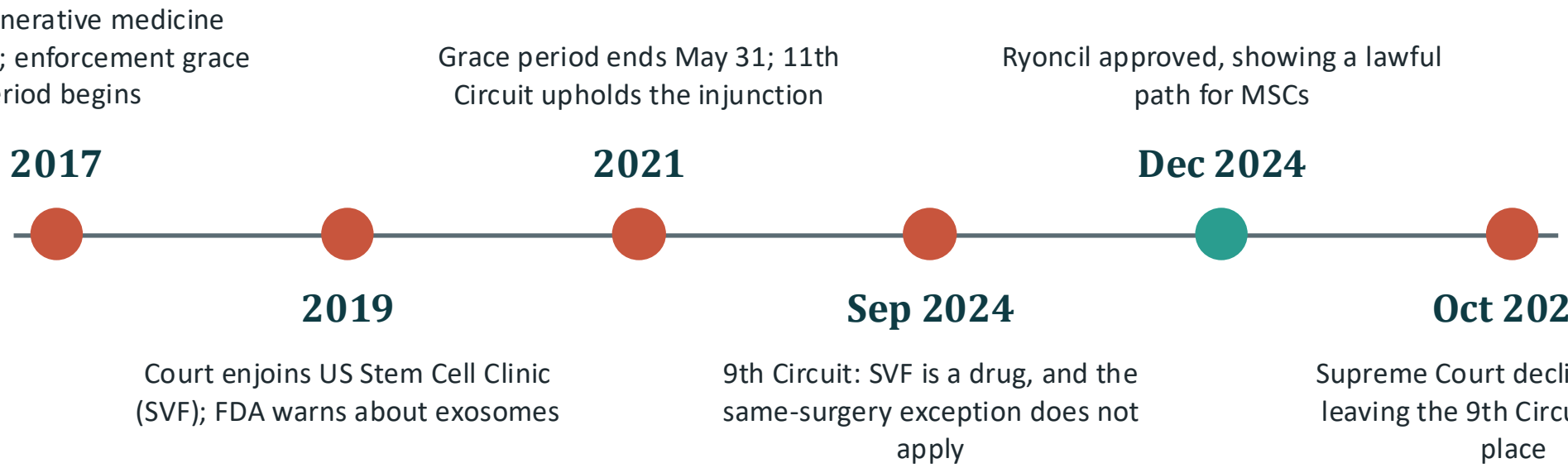
If any criterion fails, the product needs:

- An IND to study it in people
- BLA approval before it can be marketed
- Examples: SVF, culture-expanded MSCs, and most amniotic, cord, and exosome products

Same surgical procedure exception: narrowly read by courts; it does not cover SVF.

PRP: made with FDA-cleared devices; musculoskeletal use is off-label practice of medicine.

Courts have consistently sided with FDA



Same-day processing doesn't exempt a product if it's more than minimally manipulated.

Unproven products have caused serious harm

Vision loss

Three women with macular degeneration had severe vision loss after adipose "stem cell" injections into both eyes.

Kuriyan et al., NEJM 2017

Spinal cord tumor

A man developed a glioproliferative mass in his spinal cord after "stem cell" infusions abroad.

Berkowitz et al., NEJM 2016

Bacterial infections

12 patients in 3 states developed serious infections after injections of umbilical cord blood products.

CDC, MMWR 2018

Exosome reactions

FDA warned the public after patients in Nebraska had serious adverse events from unapproved exosome products.

FDA safety notification, 2019

Red flags

- Treats many unrelated conditions with one product
- Relies on testimonials instead of published data
- Says "FDA registered" or "FDA compliant" as if it meant approved
- Charges patients to join a "study"
- Promises no risk or guaranteed results
- Uses donor amniotic, cord, or exosome products
- Offers IV, spinal, or eye injections
- Pushes same-day payment or seminar "discounts"

Questions patients should ask any clinic



Six questions to ask before paying for any treatment

Consider printing these for patients who are thinking about a regenerative treatment.

1. What exactly will be injected, and where does it come from?
2. Is it FDA-approved for my condition, or part of an IRB-approved trial?
3. What published evidence supports it for my condition?
4. Who does the procedure, and is imaging guidance used?
5. What is the total cost, and what if it doesn't work?
6. Who manages complications, and how do I reach them?

How to talk with patients who ask

ON PRP

"PRP has reasonable evidence for some knee and tendon problems. It isn't a cure, and insurance usually won't pay."

ON STEM CELL CLINICS

"Most stem cell treatments advertised for many conditions aren't FDA-approved, and some have hurt people."

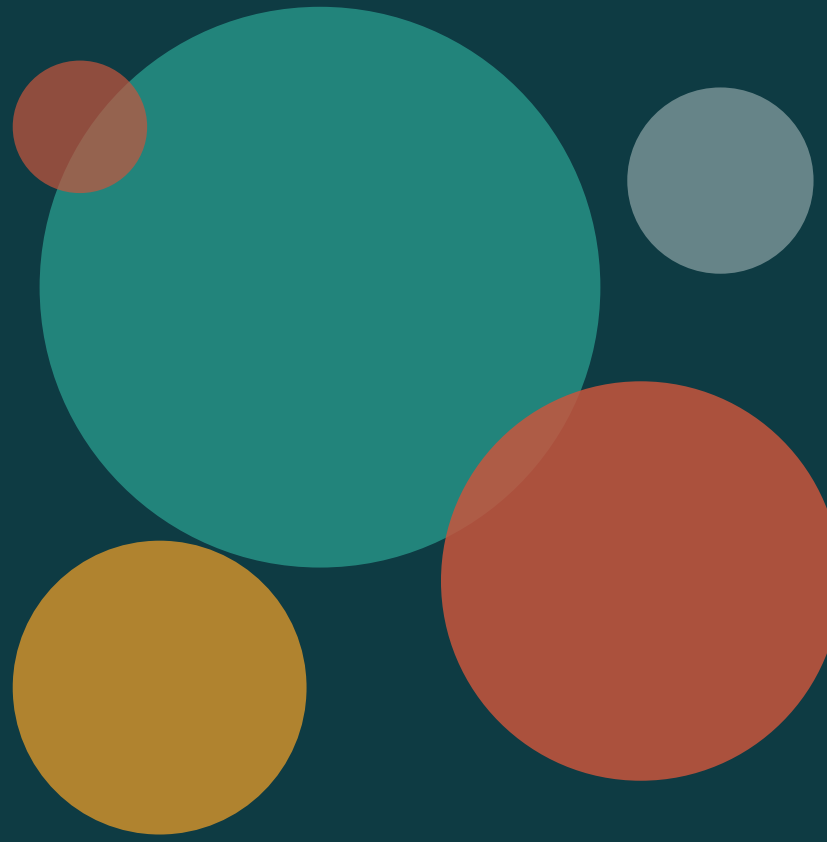
ON NEXT STEPS

"Let me refer you to someone who will tell you honestly whether it's right for you."

Avoid dismissing the question outright. Patients who feel brushed off often go to a clinic anyway, without your guidance.

05

Sample Cases



Case 1: Mild to moderate knee OA, short steroid relief

CASE 1

58-year-old teacher

- Medial knee pain for 2 years; KL grade 2
- 8 months of PT and home exercise; lost 10 lb
- Topical diclofenac helps a little
- Two steroid injections, about 6 weeks of relief each
- Wants to keep hiking

Good PRP candidate: refer

Why

- Mild to moderate OA with documented conservative care
- Steroid relief is short, and repeated steroids carry a structural cost
- Clear functional goal

Set expectations

- Benefit is modest and not guaranteed; onset in 6–12 weeks
- Self-pay, roughly $500–$2,500 per injection
- Keep strengthening before and after

Case 2: End-stage OA and a stem cell seminar

CASE 2

72-year-old retired machinist

- Bilateral knee OA, KL grade 4 with varus deformity
- Night pain; walks with a cane
- Went to a free dinner seminar on stem cells
- Quoted $8,000 for amniotic stem cell injections, due today

Refer to orthopedics, not orthobiologics

Why

- Advanced OA is unlikely to respond to any injection
- Amniotic products often contain no living cells and aren't FDA-approved for OA
- Seminar sales and same-day payment are red flags

Next steps

- Arthroplasty evaluation
- Bridge with PT, bracing, walking aids, and steroid or HA
- Give the six-questions handout

Case 3: A runner with chronic Achilles pain

CASE 3

41-year-old recreational runner

- Midportion Achilles pain for 9 months
- Has only stretched and rested
- No structured loading program yet
- Asks for PRP after a friend had a good result

Not yet: start a loading program first

Why

- PRP was no better than sham for chronic Achilles tendinopathy (ATM trial)
- Progressive loading is first-line and often works
- Conservative care hasn't really been tried

Next steps

- 12 weeks of PT-guided eccentric or heavy slow resistance loading
- Consider referral

Key takeaways

1. **PRP is a reasonable self-pay option:** for mild to moderate knee OA and some tendinopathies, after conservative care.

2. **Evidence and guidelines conflict:** use shared decision-making and set expectations about cost and benefit.

3. **Cell-based injections are not proven:** Does not imply that are not effective and can be in the right setting.

4. **Donor and exosome products are largely unapproved:** steer patients away and share the red flags.

5. **A good referral is complete:** conservative care, imaging, medications, goals, and a cost discussion.

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Questions?

