Osteoarthritis Update

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Rheumatology

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Enterprise Clinical S

United Healthcare | Optum Health Education™

Osteoarthritis Burden

- An estimated 240 million individuals worldwide have symptomatic osteoarthritis, including 10% of men and 18% of women aged 60 and older.
- High global cause of disability and chronic pain.
- Substantial health and suicidal cost directly and because of impaired work productivity and early retirement.

Bannuru RR, et al. *Osteoarthritis and Cartilage*, 2019.

Osteoarthritis Research Society International. Osteoarthritis: A Serious Disease, submitted to the U.S. Food and Drug Administration. 2016. https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf. Accessed March 27, 2019.

Centers for Disease Control and Prevention. 2003 National Health Interview Survey; 2030 Census projected population. Available at https://www.cdc.gov/arthritis/data_statistics/national-statistics.html. Accessed January 19, 2019.

United States Bone and Joint Initiative. The Burden of Musculoskeletal Diseases in the United States (BMUS). In: In. Fourth ed. Rosemont, IL. 2018: Available at https://www.boneandjointburden.org/fourth-edition. Accessed June 12, 2019.

Risk Factors

Person-level Factors	Joint-level Factors
• Age • Sex • Race/Ethnicity • Socioeconomic Status • Rural Residence • Family History and Genetic Factors • Obesity • High Blood Pressure (Mixed evidence) • High Bone Mineral Density	• Joint Injury • Joint malalignment (Mixed evidence) • Joint Deformity/Abnormal Joint Shape • Muscle Weakness (Mixed evidence) • Leg length Inequality • Physically Demanding Occupational Tasks • Elite sports

Allen KD, at al. *Osteoarthritis Cartilage*. 2022.

Definitions

►Disease of movable joints characterized by cell stress and extracellular matrix degradation.

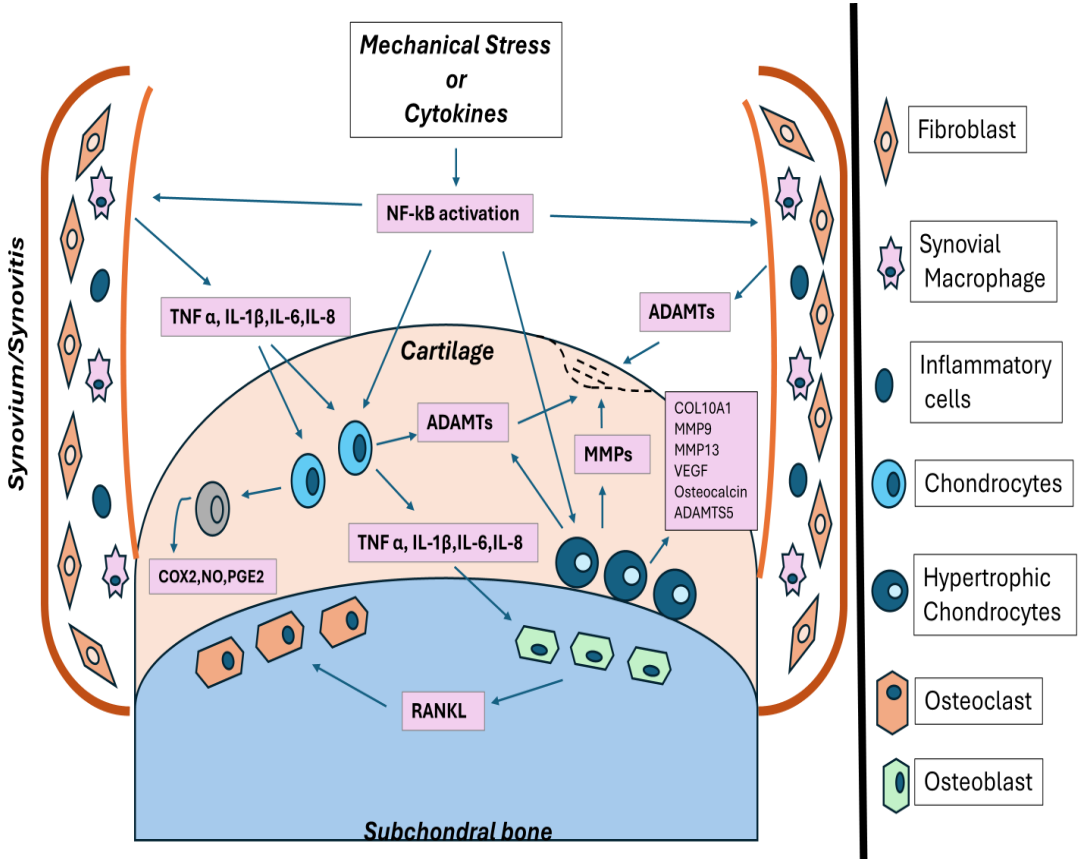
►Starts as micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity.

► Manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), resulting in illness.

Standardization of Osteoarthritis Definitions | Osteoarthritis Research Society International (OARSI) Osteoarthritis Cartilage. 2015 Apr 9. pii: S1063-4584(15)00899-7. doi: 10.1016/j.joca.2015.03.036.

Definitions

- Cell stress
- Extracellular matrix degradation initiated by micro- and macro-injury
- Activation of maladaptive repair responses
  - Pro-inflammatory pathways

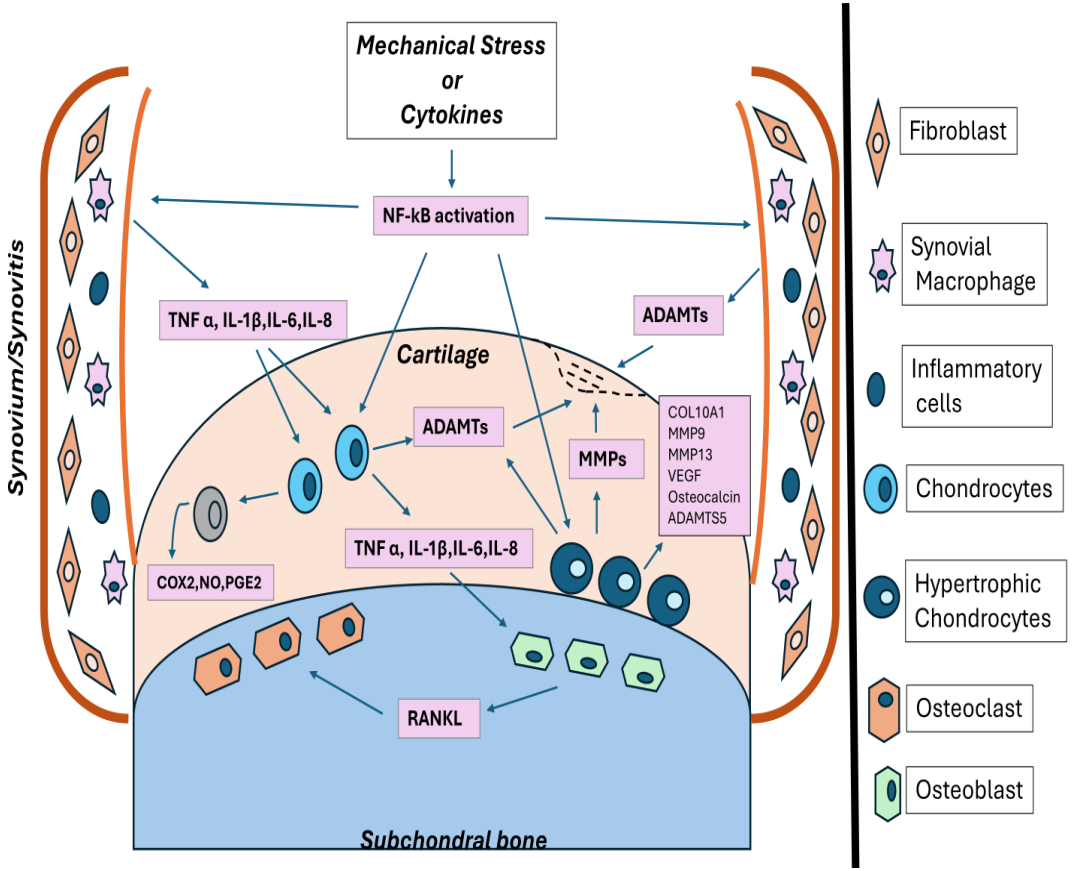


Standardization of Osteoarthritis Definitions | Osteoarthritis Research Society International (OARSI) Osteoarthritis Cartilage. 2015 Apr 9. pii: S1063-4584(15)00899-7. doi: 10.1016/j.joca.2015.03.036.

Definitions

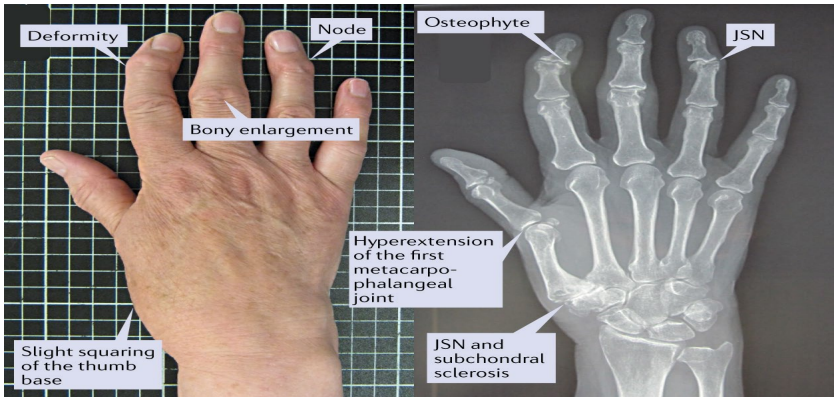
- molecular derangement
  - abnormal joint tissue metabolism

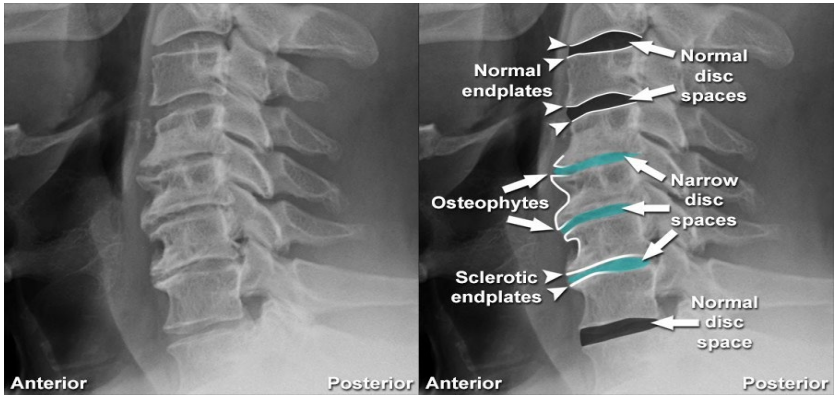
- anatomic, and/or physiologic derangements
  - cartilage degradation
  - bone remodeling
  - osteophyte formation
  - joint inflammation
  - loss of normal joint function



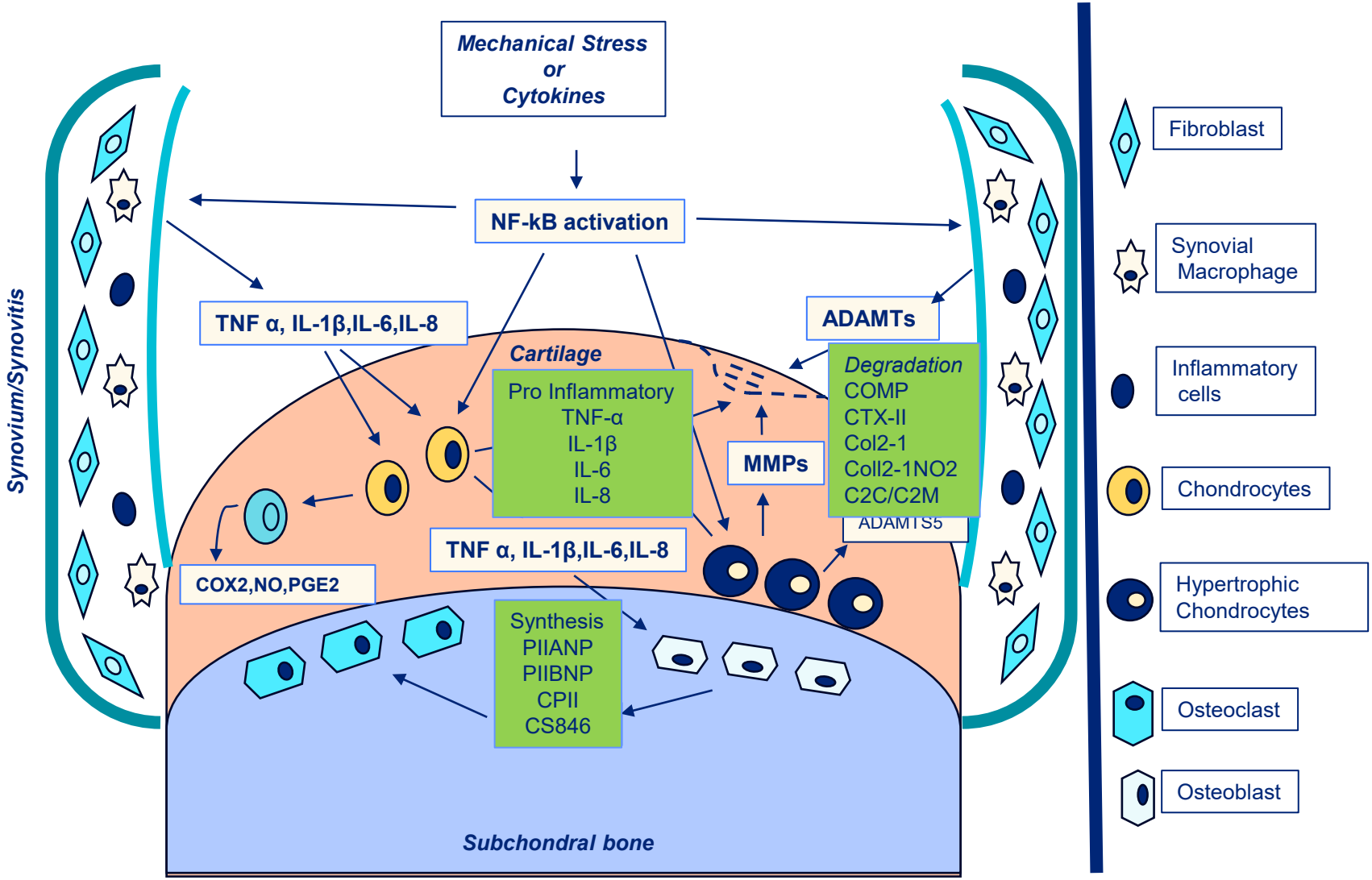
Standardization of Osteoarthritis Definitions | Osteoarthritis Research Society International (OARSI) Osteoarthritis Cartilage. 2015 Apr 9. pii: S1063-4584(15)00899-7. doi: 10.1016/j.joca.2015.03.036.

Clinical and Radiographic Characteristics





BIOMARKERS



Bernotiene E, et al. *Front. Med.* October 2020 Sec. Rheumatology Volume 7 – 2020.

BIOMARKERS

X-RAY/ ULTRASOUND

Structural

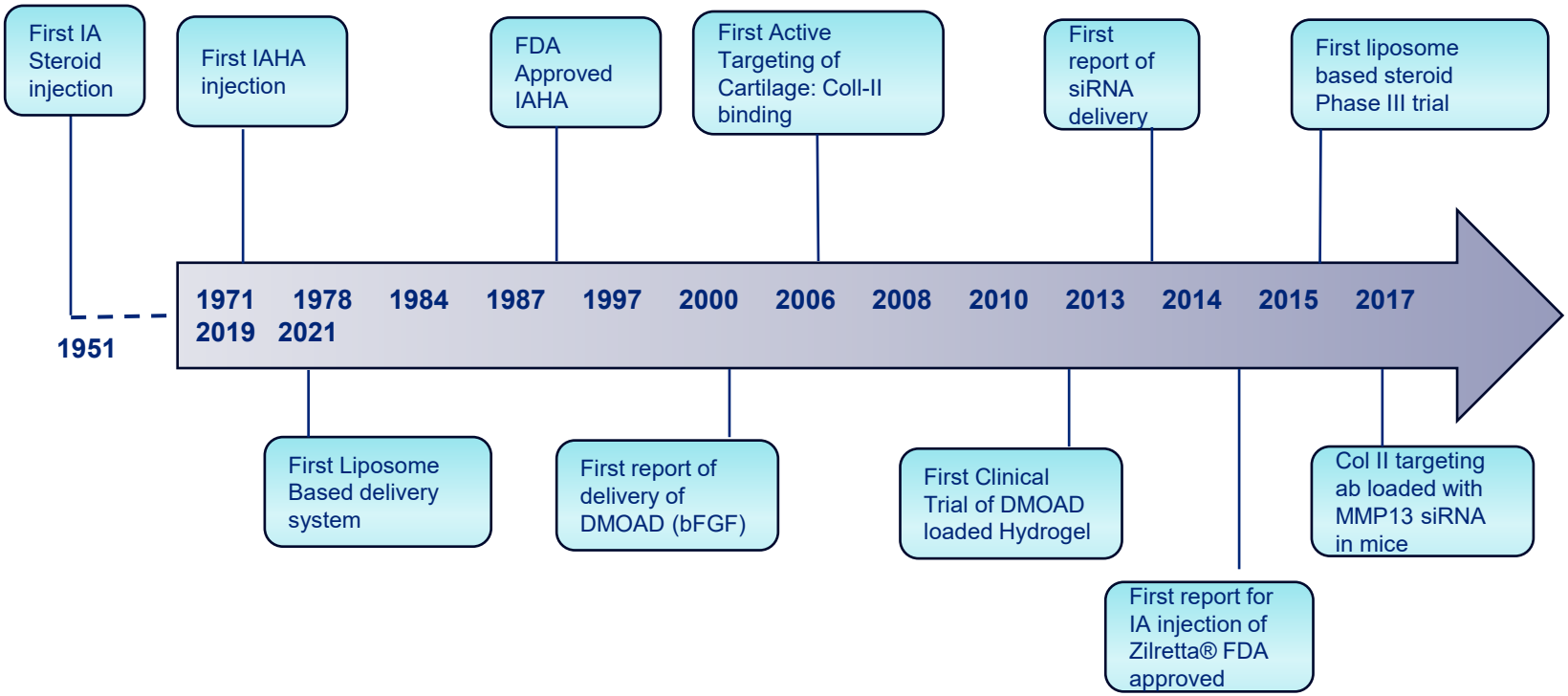
- X-ray defined joint space narrowing
- Trabecular morphometry
- Ultrasound defined synovitis and effusion

MRI

- Morphological
  - Cartilage thickness/Cartilage volume, Bone area, Bone shape
- Structural
  - Bone marrow lesions, cartilage defects, meniscal and ligament lesions
- Compositional
  - T1-rho-T2 maps

Antony B, Singh A. *Diagnostics*. 2021.

Treatment



Gao J et al. *Trends Pharmacol Sci*. 2022.

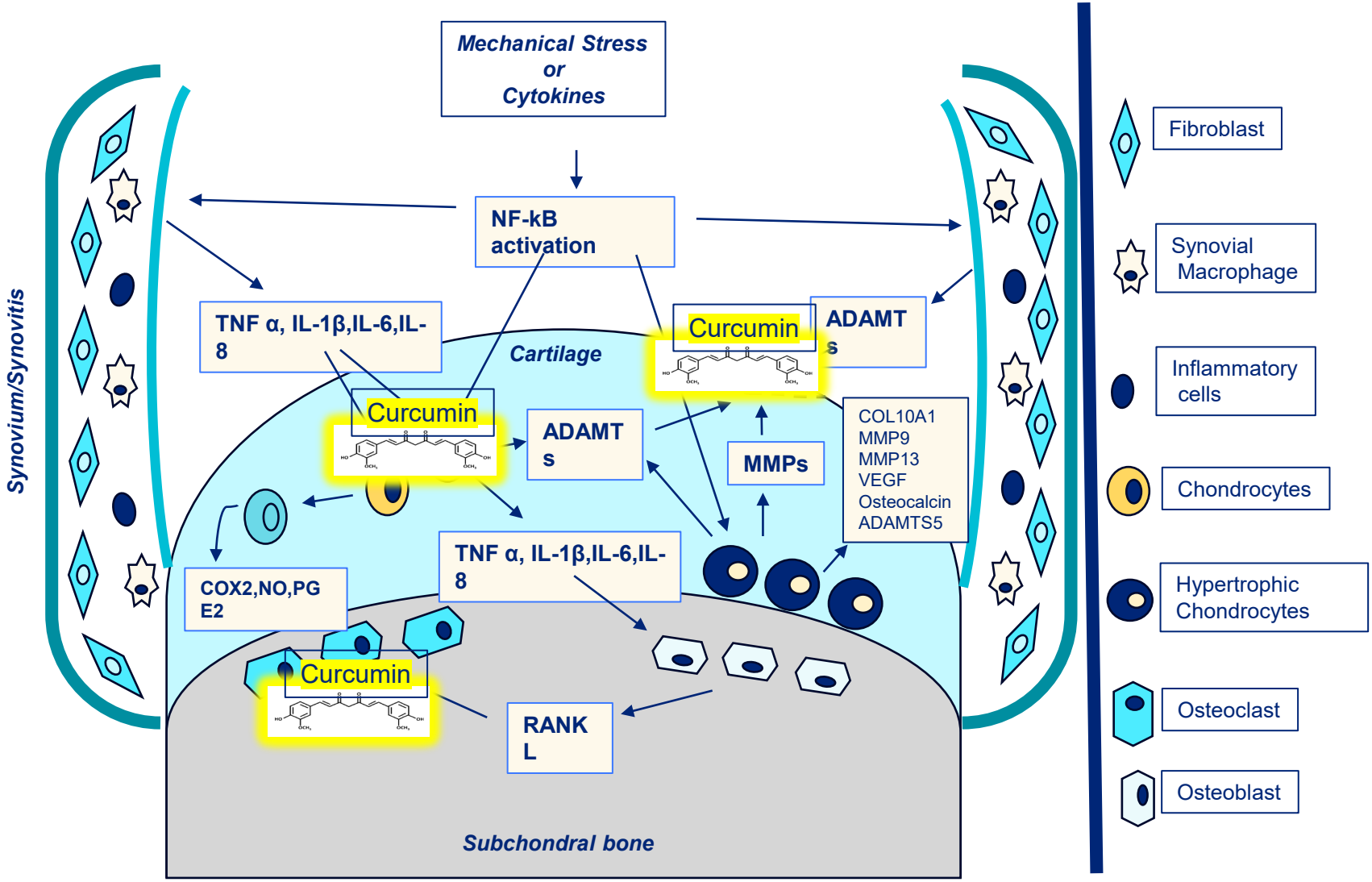
Treatment

Treatment Selections, by Level of Recommendation, for Polyarticular Osteoarthritis

Recommendation level	Strength	Treatment Type	No Comorbidities	Gastrointestinal	Cardiovascular	Frailty	Widespread pain/Depression
CORE	**Strong**	Arthritis Education; Structured Exercise Programs (Type 1- strengthening and/or cardio and/or balance training/neuromuscular)					
Level 1A- *≥75% "in favor" & >50% "strong" Recommendation*	**Strong**	***Pharmacologic***	*refer to Level 1B*	*refer to Level 1B*		*refer to Level 1B*	*refer to Level 1B*
		Non-Pharmacologic	*refer to Level 1B*	*refer to Level 1B*		*refer to Level 1B*	*refer to Level 1B*
Level 1B- *≥75% "in favor" & >50% "conditional" Recommendation*	**Conditional**	***Pharmacologic***	Non-selective NSAIDs Topical NSAIDs	COX-2 Inhibitors	*see below*	*see below*	*see below*
		Non-Pharmacologic	Mind-body Exercise, Dietary Weight Management (with or without Exercise), Self-Management Programs, Gait Aids	Mind-body Exercise, Dietary Weight Management (with or without Exercise), Self-Management Programs, Gait Aids		Mind-body Exercise, Self-Management Programs, Gait Aids	Mind-body Exercise, Cognitive Behavioral Therapy, Dietary Weight Management (with or without Exercise), Self-Management Programs
Level 2- *60%-74% "in favor"*	**Conditional**	***Pharmacologic***	• Non-selective NSAID+PPI • COX-2 Inhibitors	Non-selective NSAID+PPI Topical NSAIDs	Topical NSAIDs	Topical NSAIDs	• Non-selective NSAIDs • Non-selective NSAID + PPI • COX-2 Inhibitors
		Non-Pharmacologic	*refer to Level 3*	*refer to Level 3*		*refer to Level 3*	Gait Aids
Level 3- *40%-59% "in favor"*	**Conditional**	***Pharmacologic***	Duloxetine	*see below*	• Non-selective NSAIDs • Non-selective NSAID + PPI • COX-2 Inhibitors	*see below*	Duloxetine
		Non-Pharmacologic	*see below*	Cognitive Behavioral Therapy alone		Cognitive Behavioral Therapy alone, Dietary Weight Management alone	Aquatic Exercise, Cognitive Behavioral Therapy with Exercise
		Nutraceutical	Curcuminoid Formulations	Curcuminoid Formulations		Curcuminoid Formulations	Curcuminoid Formulations

Bannuru RR, et al. *Osteoarthritis and Cartilage.* 2019.

Curcumin



Mohammadian Haftcheshmeh S et al. *Rev Physiol Biochem Pharmacol*. 2021.

Treatment

Level 4B- *60%-74% "against"*	**Conditional**	***Pharmacologic***	IACS, IAHA	Duloxetine, IACS	Duloxetine, IACS	• Non-selective NSAIDs • Non-selective NSAID + PPI • COX-2 Inhibitors IACS	IACS, IAHA
		Non-Pharmacologic	Aquatic Exercise, Cognitive Behavioral Therapy (with or without Exercise)	Aquatic Exercise, Cognitive Behavioral Therapy with Exercise		Cognitive Behavioral Therapy with Exercise, Dietary Weight Management with Exercise	Massage
		Nutraceutical	Avocado Soybean Unsaponifiables, Boswellia	*refer to Level 4A*		Avocado Soybean Unsaponifiables, Boswellia, Vitamin D	Avocado Soybean Unsaponifiables, Boswellia
Level 4A- *≥75% "against" & >50% "conditional" Recommendation*	**Conditional**	***Pharmacologic***	Oral Opioids, Paracetamol	IAHA, Non-selective NSAIDs, Paracetamol	IAHA, Paracetamol	Duloxetine, IAHA, Paracetamol	Paracetamol, Topical NSAIDs
		Non-Pharmacologic	Balneotherapy, Conventional Acupuncture, Massage, Mobilization & Manipulation, Therapeutic Ultrasound, Thermotherapy (hot), Wedge Insoles	Balneotherapy, Electrical Stimulation, Massage, Mobilization & Manipulation, Therapeutic Ultrasound, Thermotherapy (hot), Wedge Insoles		Aquatic Exercise, Balneotherapy, Conventional Acupuncture, Massage, Mobilization & Manipulation, Therapeutic Ultrasound, Thermotherapy (hot), Wedge Insoles	Balneotherapy, Conventional Acupuncture, Mobilization & Manipulation, Therapeutic Ultrasound, Wedge Insoles
		Nutraceutical	Collagen, Diacerein, Glucosamine + Chondroitin, Methylsulfonylmethane, Vitamin D	Avocado Soybean Unsaponifiables, Boswellia, Chondroitin, Collagen, Conventional Acupuncture, Diacerein, Glucosamine + Chondroitin, Methylsulfonylmethane, Vitamin D		Collagen, Glucosamine + Chondroitin, Methylsulfonylmethane	Chondroitin, Collagen, Glucosamine + Chondroitin, Methylsulfonylmethane, Vitamin D

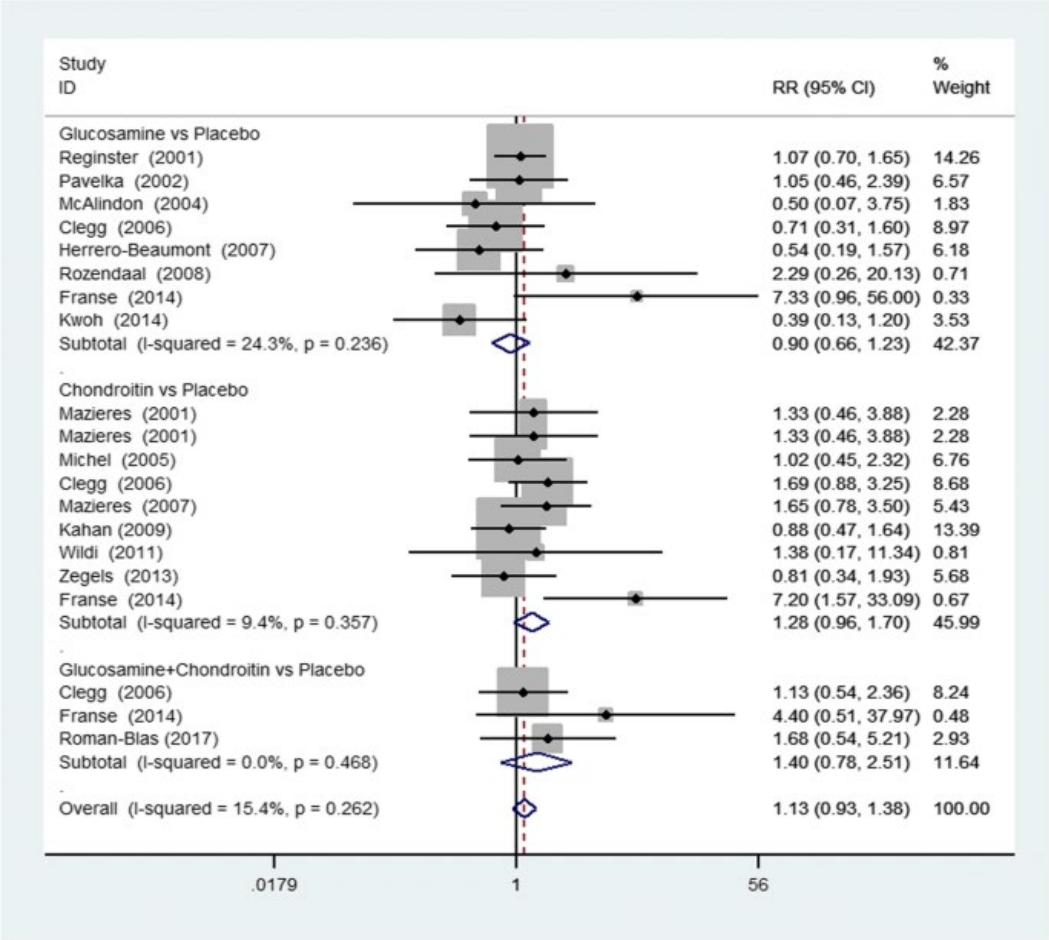
Bannuru RR, et al. *Osteoarthritis and Cartilage*, 2019.

Intra Articular Hyaluronic Acid

Author	Year	Study type	HA brand	Comparison group	Outcome measures assessed	Follow up	Conclusion
Yu et al. [61]	2018	RCT-DB	PRP	HA, PRP+HA, Placebo	WOMAC, Karnofsky perfo	52 wks. Po	Improvement significant in PRP+HA group
Lamo Espinosa et al. [62]	2018	RCT-NB LT	BM-MSCs-LD/HD +HA	HA alone (Hyalone)	VAS, WOMAC	12-48 mon	Safe and feasible with long term clinical improvement
Hangody et al. [63]	2018	RCT-DB	Cingal (HA+TA)	Monovisc (1000-2900 kDa), saline	PGA, WOMAC	26 WKS	Effective, immediate and LT relief with Cingal > 26 wks
Wang et al. [64]	2018	RCT-DB	HA+CS (betamethasone)	HMWHA	VAS, WOMAC	6 months	Improvement, rapid in HA+CS group
Buendia et al. [65]	2018	RCT-SR	LP-PRP-1	HA (Durolane), NSAID	VAS, WOMAC, MRI, X-RAY	6-12 mont	Improvement better in LP-PRP group at 52 wks.
Hermans et al. [66]	2019	RCT-OL	Hylan (G-F 20)	UC (usual care)	KOOS, PGA	52 wks.	Effective
Maheu et al. [67]	2019	RCT-DB	Ostenil1 Plus	Hyalan G-F 20	WOMAC	6 months	Effective and non-inferior
Takamura et al. [68]	2019	RCT-SB	Gel-200 (XLHA)	Saline	VAS, WOMAC	26 wks.	Effective and clinical improvement
Tavassoli et al. [69]	2019	RCT-SB	PRP-1	PRP-2, HA-3 (Hyalgan)	VAS, WOMAC	12 wks.	Improvement, PRP better than HA
Di Martino et al. [70]	2019	RCT-DB	PRP	Hylubrix (HA)	VAS, IKDC, EUROQoL	24 mn & M	Effective, not superior in PRP group
Bahrami et al. [71]	2020	RCT-SB	HMWHA (Arthromac)	LMWHA (3 inj.)	VAS, WOMAC, LKI	2-6 month	Remarkable improvement both group with no difference
Kesiktas et al [72]	2020	RCT-SR	Prostrolane (Peptide)	HA (Biometics), PRP	VAS, WOMAC, HAQ	3 months	Significant improvement, better in peptide group
Mochizuki et al. [73]	2020	RCT-SB	Artz (LMWHA)	Suvenyl (IMMWHA) (1500-3900)	VAS, JKOM	6 wks.	Significant efficacy. No difference

Chavda S et al. *Cureus*. 2022.

Glucosamine Chondroitin



Zhu X. et al. *J Orthop Surg Res.* 2018

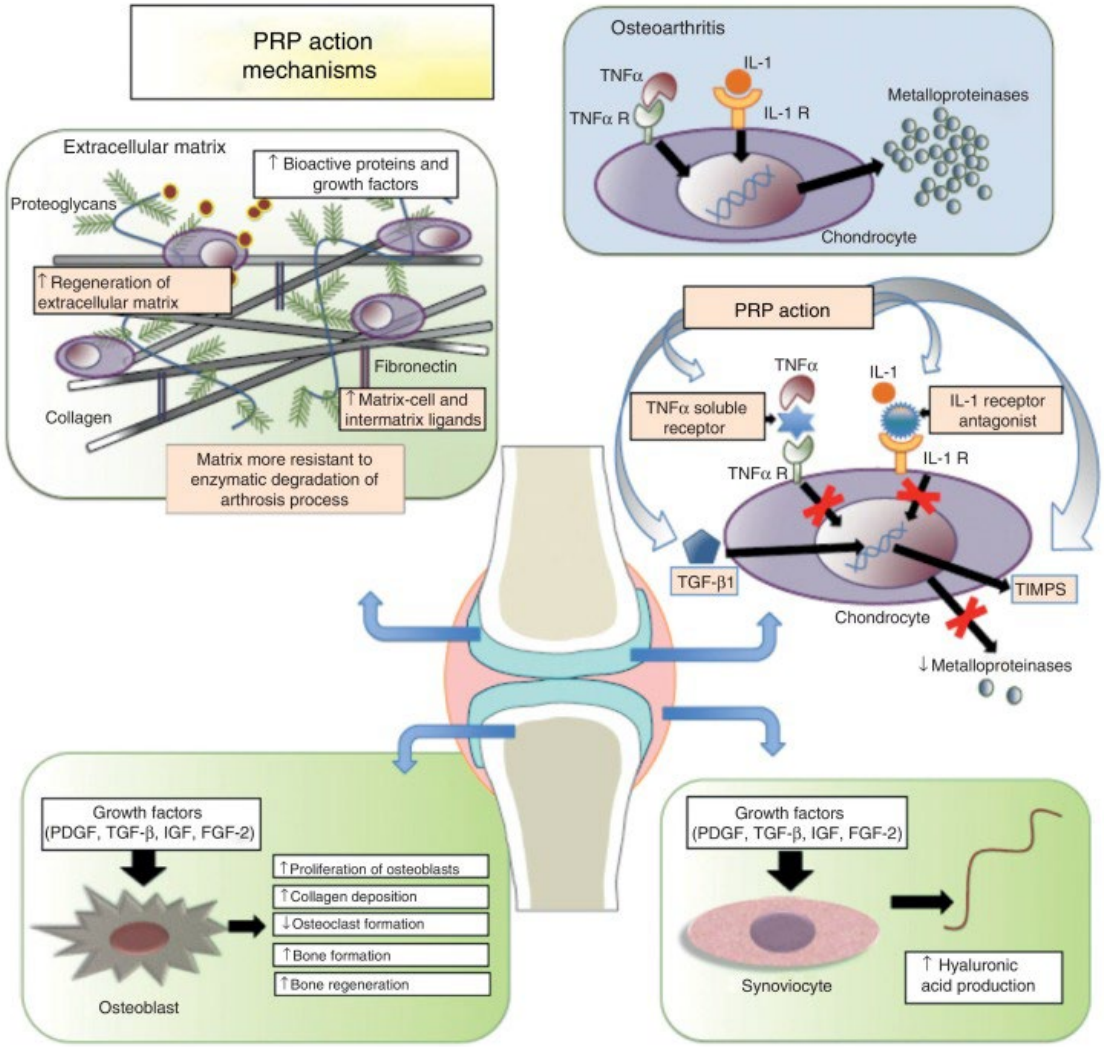
Treatment	Rationale
Bisphosphonates	No efficacy
Calcitonin	No efficacy
Chondroitin	Low quality evidence
Colchicine	Potential for GI toxicity, no efficacy
Collagen	No efficacy
Dextrose Prolotherapy	Low quality evidence
Diacerein	Unfavorable safety/efficacy profile
Doxycycline	No efficacy
Electrical Stimulation	Low quality evidence from trials with very small sample sizes and short follow-up
Electroacupuncture	Unfavorable efficacy/safety profile

Bannuru RR, et al. *Osteoarthritis and Cartilage*, 2019.

Treatment	Rationale
Glucosamine	No efficacy
Glucosamine & Chondroitin	No efficacy
IA Stem Cells	Low quality evidence, no safety data provided, potential safety concerns, uncertainty regarding specific stem cell formulations utilized
IL-1 Receptor Antagonists	No efficacy
Kinesio Taping/Strapping	No efficacy
Laser Acupuncture	No efficacy, implausible biological mechanism
Laser Therapy	No efficacy, implausible biological mechanism
Massage	Lack of evidence
Methotrexate	No efficacy
Nerve Block Therapy	Lack of long-term efficacy/safety data
(Omega-3/6) Poly-Unsaturated Fatty Acids	Lack of evidence

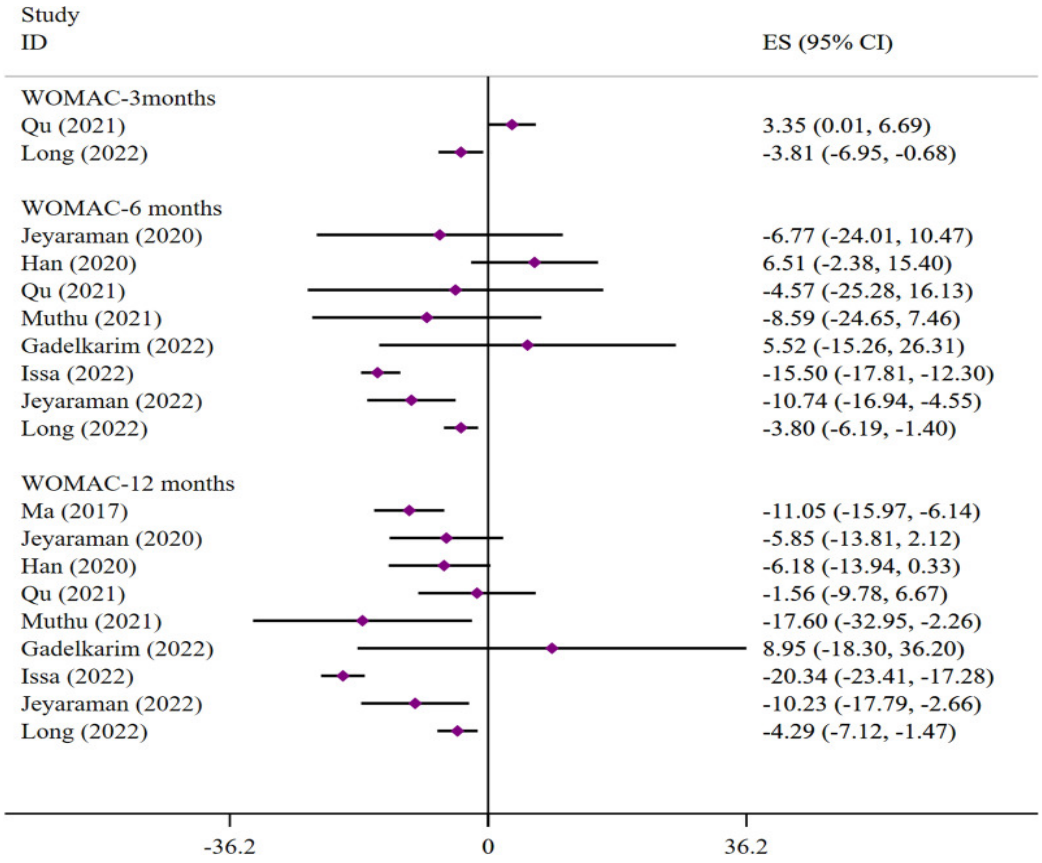
Bannuru RR, et al. *Osteoarthritis and Cartilage*, 2019.

Platelet Rich Plasma



Everts P, et al. *Int J Mol Sci*. 2020
Knopp E et al. *Revista Brasileira de Reumatologia (English Edition)*. 2016.

Stem Cell Injection



Shang Z, et al. *Stem Cell Res Ther*. 2023.

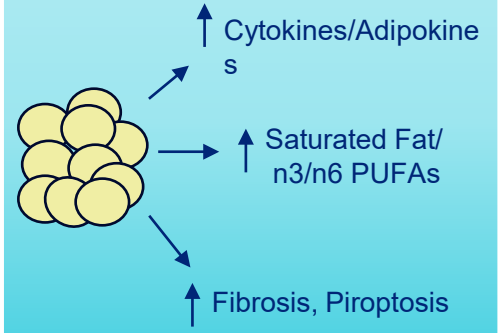
Treatment	Rationale
Oral Opioids strongly not recommended over NSAIDs	Unfavorable efficacy/safety profile
Orthopedic Footwear	Low quality evidence, no efficacy
Patellar Taping	No efficacy
PRP	Low quality evidence
Pycnogenol	Low quality evidence
Realigning Patellofemoral Brace	No efficacy, low quality evidence
Soft Braces/Knee Sleeves	Low quality evidence
Statins	No data
Strontium	Toxicity, approval concerns
Therapeutic Ultrasound	Low quality evidence, implausible physiological rationale for use in deep joint locations
Thermotherapy (cold)	Low quality evidence
Thermotherapy (hot)	Low quality evidence
TNF-α Inhibitors	No data
Topical Capsaicin	Unfavorable efficacy/safety profile
Transdermal Opioids	Unfavorable efficacy/safety profile
Varus/Valgus Unloading/Re-alignment Brace	Low quality evidence, no evidence of benefit for widespread pain
FX006 strongly not recommended over IACS	Traditional IACS were recommended over FX006, but the use of traditional IACS was controversial in hip and polyarticular OA, therefore the use of FX006 was strongly not recommended.

Bannuru RR, et al. *Osteoarthritis and Cartilage*, 2019.

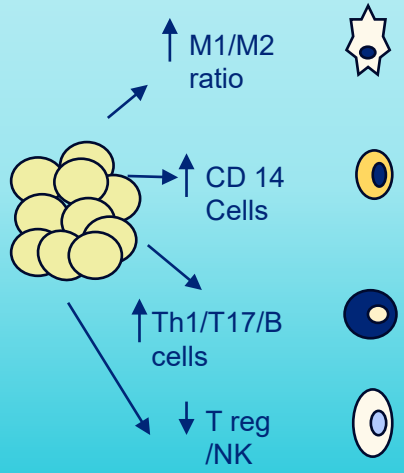
Obesity

Increased Joint Load

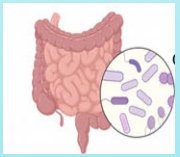
Promotion of inflammatory Responses



Impairment in immune System



Dysbiosis



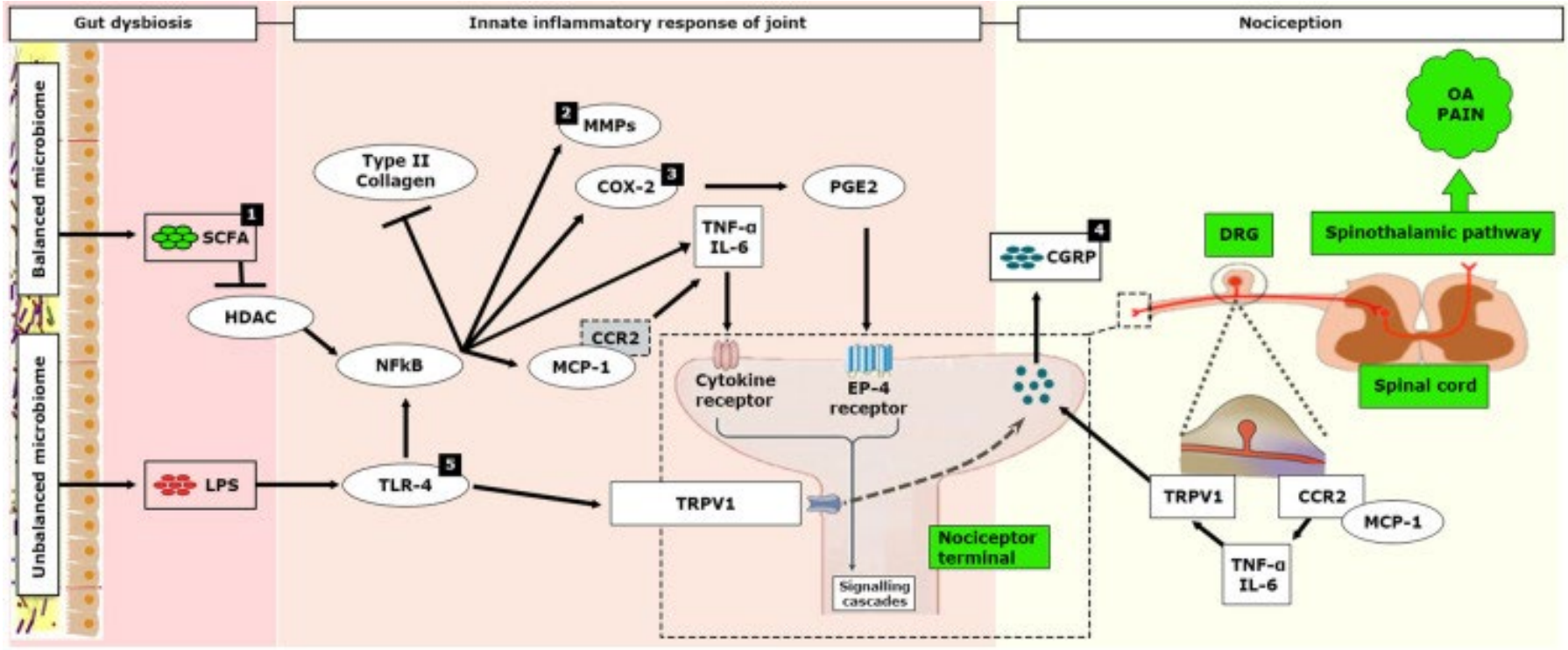
Bacterial Diversity

Recruits & Activates Inflammatory cells

LPS endocannabinoid system

Gambari L, et al. *Int. J. Mol. Sci*. 2023.

Probiotics



Rahman SO, et al. *Curr Rheumatol Rep*. 2023.

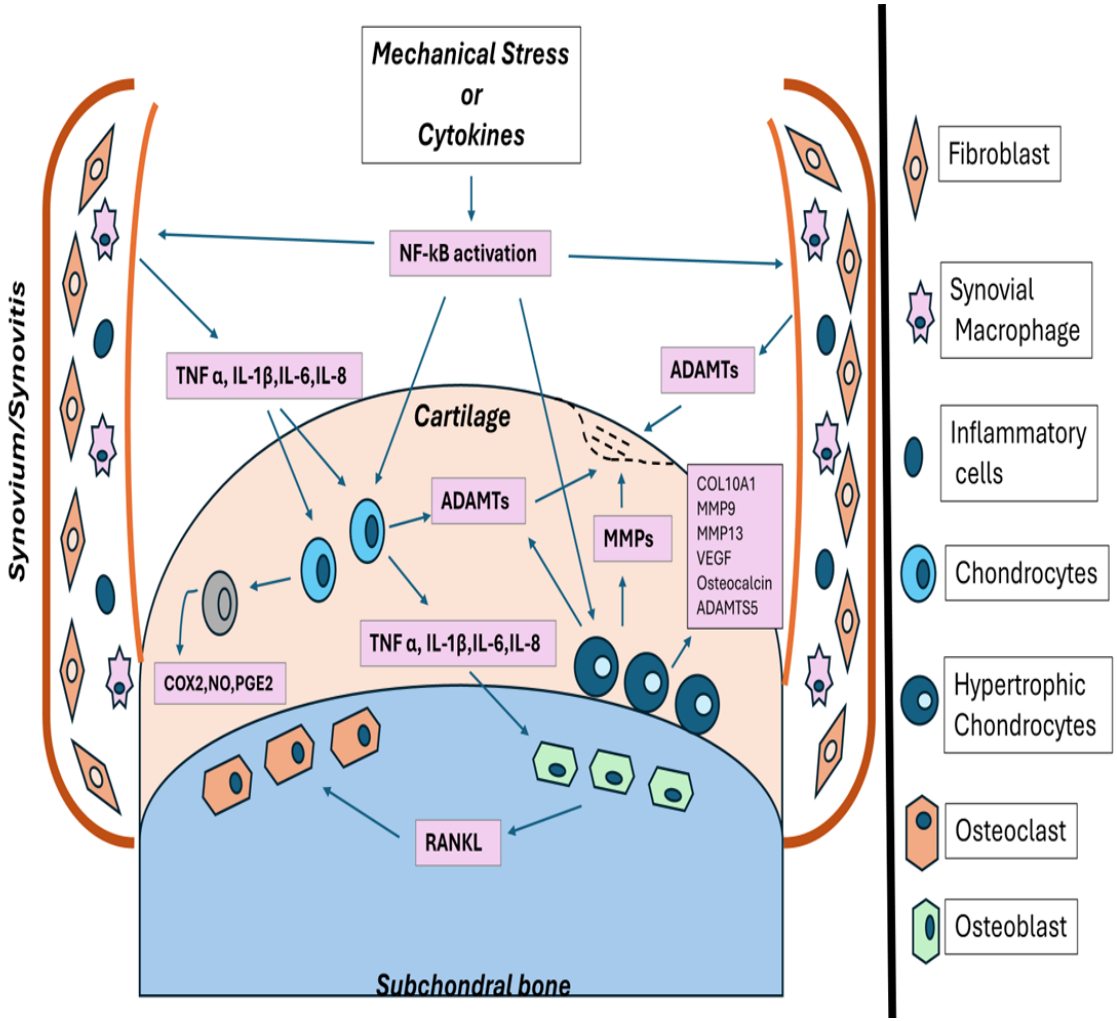
Probiotics

Probiotic strain(s)	Dose; duration	Results			
		Pain behavior	Dorsal root ganglion	Synovium	Cartilage
Monosodium iodoacetate (MIA)–induced OA					
Lactobacillus acidophilus [12]	NA; 15 days	↑ PWL; PWT; WBC	↓ TRPV-1 expression; CGRP release	↓ TNF-α; IL-6; MMP3	↓ OARSI and total Mankin Score
				↑ IL-10; TIMP3	
Lactobacillus acidophilus [13]	125 mg/ml (2 × 1011 CFU/ml)/day; 24 days	↑ PWL; WBC	↓ TRPV-1 expression; CGRP release	↓ TNF-α; IL-1β; MCP-1 MMP-13	↑ GPR43 + cells
Lactobacillus rhamnosus [14]	NA; 28 days	↑ PWL; PWT; WBC	↓ MCP-1 and CCR2	↓ MCP-1 and CCR2	↓ OARSI and total Mankin score
			↑ GABA release and PPAR-γ expressi	↑ IL-10; TIMP3	
Lactobacillus casei [15]	2 × 1010 CFU/kg/day; 8 weeks	↑ PWT	-	↓ COX-2; TNF-α; IL-6; IL-1β; MMP1,3 & 1	↓ COX-2; TNF-α; IL-6; IL-1β; MMP1,3 & 13
				↑ TIMP1	↑ TIMP1
Clostridium butyricum [16]	1010 CFU/day; 2 weeks (pre-treatment) and 4 weeks (post-treatme	↑ WBC	-	-	↓ TIMP1 and 3; MMP2,3,9 and 13; OARSI score
Anterior cruciate ligament transection (ACLT)–induced OA					
Clostridium butyricum [17]	100 mg/kg/day (5.5 × 107 CFU/g); 6 weeks	↑ WBC	-	↓ IL-1β; TNF-α	↓ OARSI scores; cartilage degeneration scores; synovial tissue inflammation scores; IL-1β;
Lactobacillus plantarum [18]	100 mg/kg (5 × 1010 CFU/kg)/day; 6 weeks	↑ WBC	-	↓ IL-1β; TNF-α	↓ OARSI scores; cartilage degeneration scores; synovial tissue inflammation scores; IL-1β;
Streptococcus thermophilus [19]	5 × 109, 5 × 1010, and 5 × 1011 CFU/kg/day; 24 weeks	↑ PWT; PWD	-	↓ Synovial score	↓ OARSI score
					↑ Type II collagen
Partial medial meniscectomy (PMM)–induced OA					
Lactobacillus acidophilus [20]	3 × 109 CFU/200 µL twice/week; 11 weeks	↑ PWT	↓ TRPV1 expression	-	↓ OARSI scores; MMP13; RUNX2

Rahman SO, et al. *Curr Rheumatol Rep*. 2023.

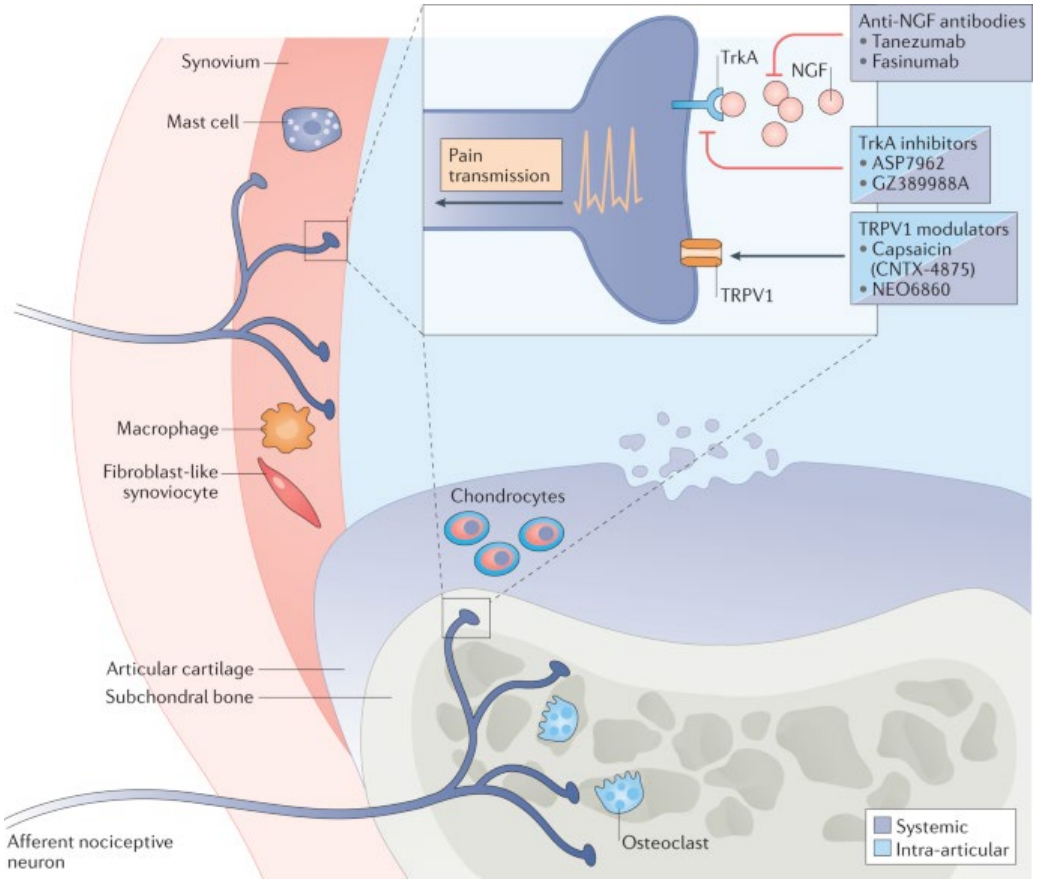
Emerging Therapies
Disease Modifying Osteoarthritis Drugs (DMOADs)

- Wnt inhibitor Phase III IA (Lorecivivint)
- TRPV1 Modulator Phase III IA
- rhFGF 18 Phase II IA
- ADAMTS5 inhibitor Phase II Oral, Phase III SC
- Cathepsin K Inhibitor Phase II Oral
- IL 6 R inhibitor IV Phase III
- CCL17 inhibitor Phase I IV
- GM-CSF inhibitor Phase II SC (Hand OA)
- Promoter endogenous Progenitor Cell Phase I



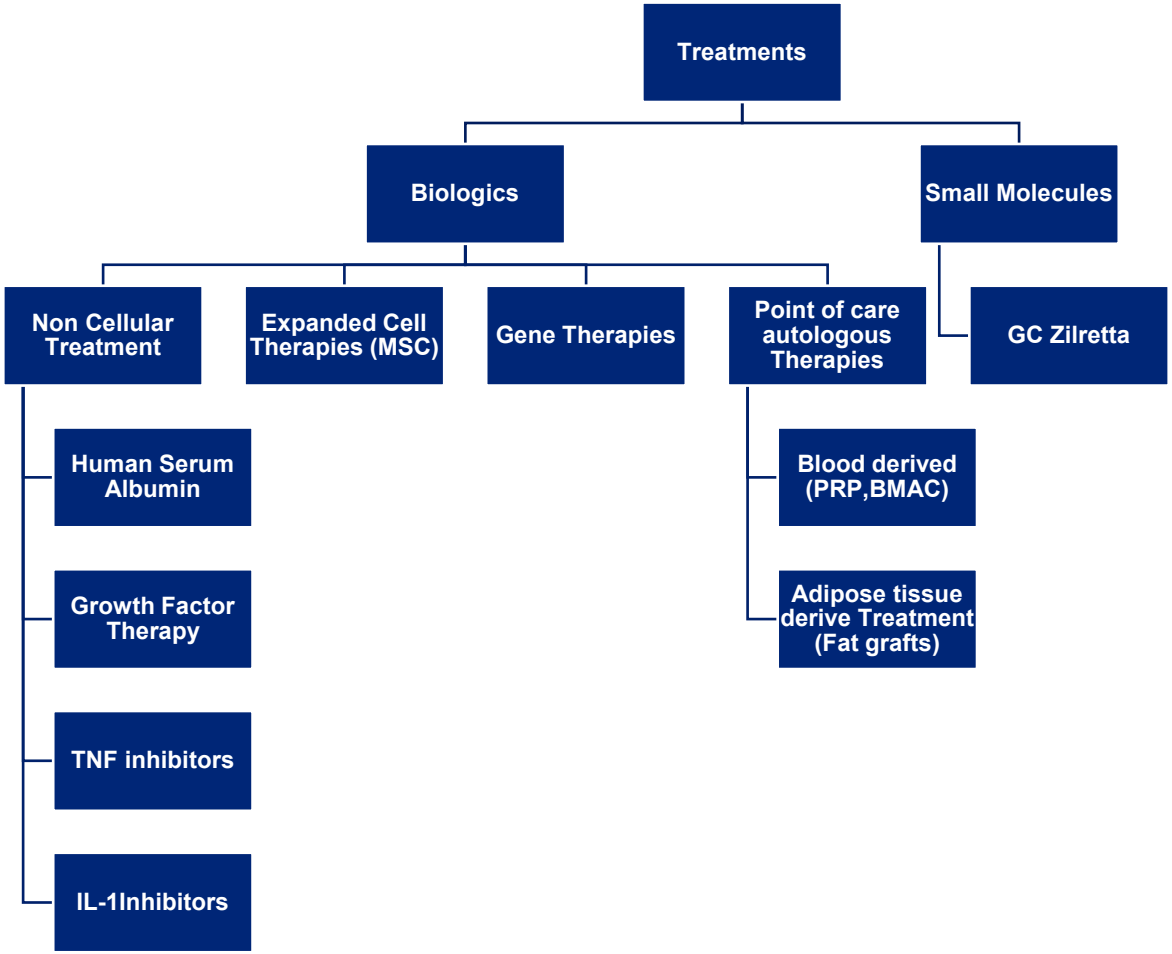
Latourte, A., et al. *Nat Rev Rheumatol.* 2020.

Pain path



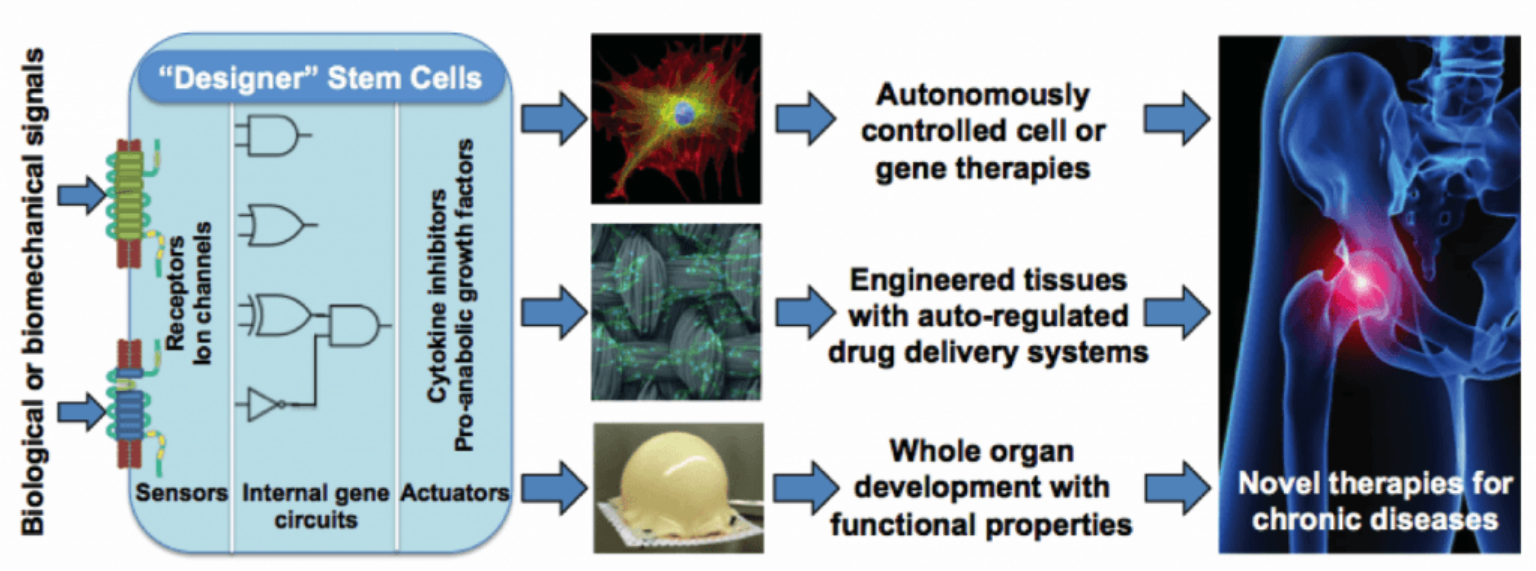
Latourte, A., et al. *Nat Rev Rheumatol.* 2020.

Intra-articular treatment options



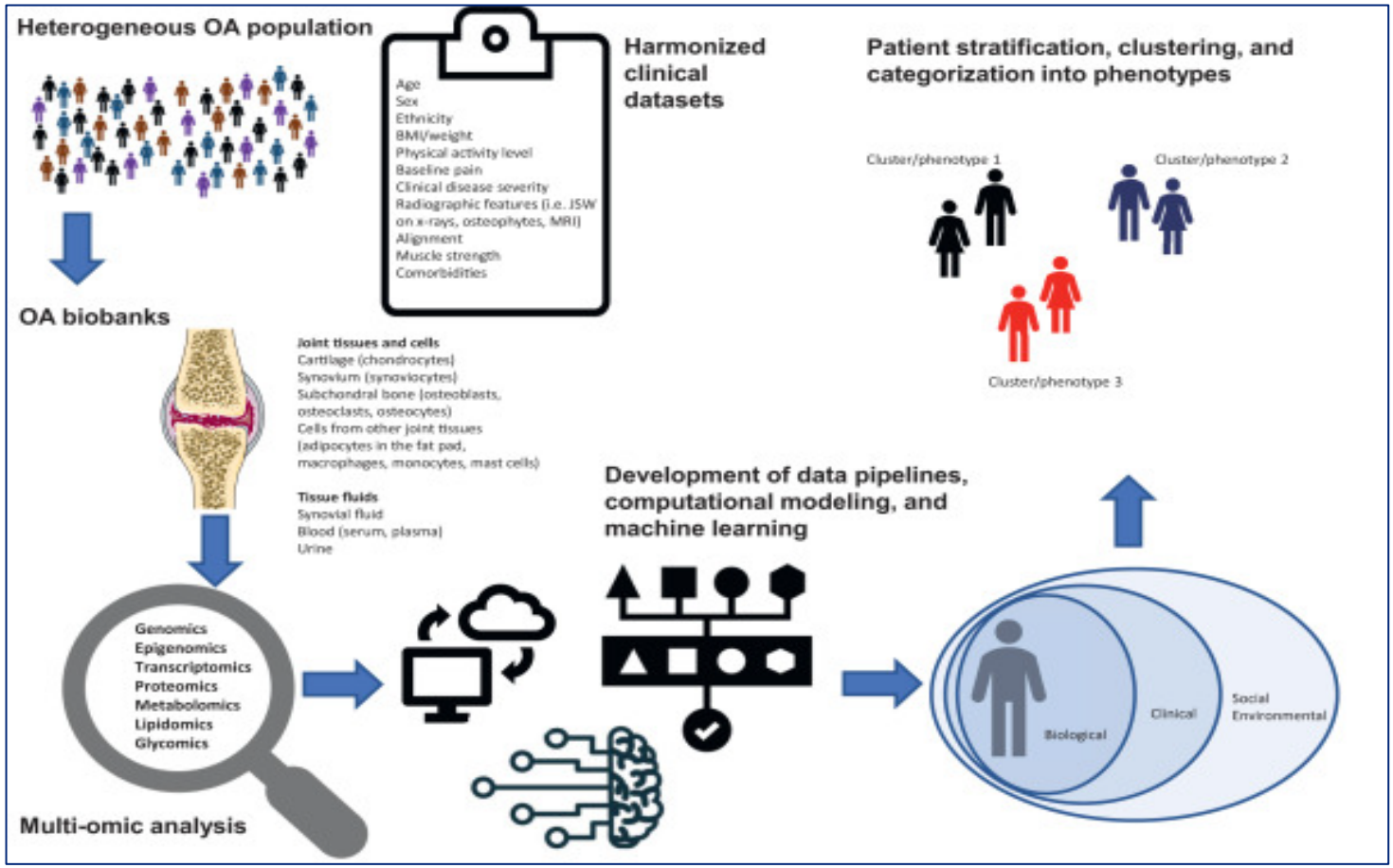
Jones, I.A., Togashi, R., Wilson, M.L. et al. Intra-articular treatment options for knee osteoarthritis. *Nat Rev Rheumatol* 15, 77–90 (2019). https://doi.org/10.1038/s41584-018-0123-4

Gene Therapy



Farshid Guilak, PhD. Washington University School of Medicine. Center for Regenerative Medicine.

Use of Artificial Intelligence



Ali M et al. *Best Practice & Research Clinical Rheumatology*. 2023.

"Doctors are men who pour drugs of which they know little, to cure diseases of which they know less, into human beings of whom they know nothing"

Voltaire

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THANK YOU!

QUESTIONS?