Q9. Should we measure pain *vs* function *vs* disability in preclinical OA models – to parallel human "OA illness"?

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Response/Recommendation: Yes. Pain, musculoskeletal function, and disability represent distinct but complementary dimensions of OA disease. As all three dimensions are relevant to patient quality of life and treatment goals, it is important to measure these outcomes to provide a comprehensive assessment of disease state and therapeutic efficacy in preclinical models.

Strength: Moderate

Delegate Vote:

Rationale:

OA symptoms: pain *and* function: Although pain may be the most significant symptom of disease for which patients seek treatment[1], other symptom domains of musculoskeletal function and disability contribute to the decline in quality of life in symptomatic patients[2]. For the purposes of this discussion, pain refers to nociceptive sensory hypersensitivity, musculoskeletal function refers to the capacity to perform physical tasks, and disability refers to the broader impact of pain and function on daily activity and behavior. While inter-related, these symptom domains are not equivalent, are commonly measured separately in clinical studies, and current OA treatment guidelines weight their importance equally[3]. Pain is a risk factor for functional decline in patients with OA[4], but pain and function have distinct contributions to disability and progression of OA[5, 6]. Although inter-related, the impact of pain on musculoskeletal function and disability varies in individual patients due to differences in pain tolerance and other physical inputs that can influence pain and function distinctly[6, 7]. These factors include musculoskeletal strength[5, 8], concomitant depression[9] and other co-morbidities and psychosocial factors[10 11, 12]. Although controlling for all these factors is beyond the scope of most preclinical animal studies, **the incorporation of outcomes related to pain, function *and* disability is possible and needs to be considered.**

In animal models, direct pain measures (nociceptive tests), functional measures (such as rearing or climbing behavior, grip strength), and other behaviors measuring global disability (gait and mobility metrics, exploratory behavior) assess fundamentally different biological processes. However, musculoskeletal function measured by behavioral tests may be related to underlying pain, and distinguishing between these categories in rodents is not always easy. Challenges with pharmacologic analgesics[13] or rehabilitative interventions[14, 15] can be used to understand and dissect effects of pain relief and functional improvement, demonstrating the importance of measuring outcomes that capture these different domains. This becomes even more important to consider in the setting of aging, due to the development of muscle strength loss[16] and changes in cognition which can impact function and disability independent of pain.

Dissociation between structure and symptoms: The severity of symptoms in OA is not strongly linked in a one-to-one fashion to the extent or severity of structural joint pathology [17, 18]. Although there are reported relationships between structure and pain[19], the inter-relationship is complex and individual patients can have severe symptoms even when structural pathology is mild, while others can have mild symptoms in the setting of advanced structural pathology[20 21]. In addition, OA joint pathology can exist in an asymptomatic state, and the prevalence of asymptomatic OA has been reported to be 19-43%[22]. Reflecting human disease, the relationship between structure and symptoms in preclinical models of OA is also complex, and varies depending on the model used [23]. For example, gait adaptations in a rat model of OA were best correlated with bony remodeling and synovitis but not cartilage loss [24, 25] – the hallmark sign of OA pathology often measured to demonstrate effectiveness of therapeutics. Moreover, interventions may differentially impact structure and pain in a model-specific manner. Access to a running wheel in the mouse DMM model of OA accelerated joint degeneration but did not cause an advance in painful symptoms[14]. Further, absence of the chemokine receptor CCR2 or its ligand CCL2 has been shown to significantly improve pain-related outcomes in this model, while having little effect on structural outcomes [13, 26]**.** Similar responses have been seen with enzyme therapies that shift local joint metabolism; here, intra-articular delivery of an indoleamine 2,3 deoxygenate fusion protein shifted both tactile sensitivity and improved gait, but did not improve joint structure[27]. Thus, joint structure cannot act as a direct surrogate for joint pain and function in preclinical studies. Novel therapies designed to primarily target structural outcomes could still be effective for symptomatic relief [28, 29 30] but this needs to be established for novel agents. *For clinical*

translatability, symptomatic disease states or phenotypes are most important to consider when developing new therapeutic strategies, and so measurement of symptomatic outcomes at the preclinical level is critical.

Recommendations: In preclinical studies, adding outcome measures of musculoskeletal pain, musculoskeletal function, and disability will improve our understanding of how underlying patterns of disease pathology and distinct cellular and molecular mechanisms relate to these important inter-related domains of symptomatic disease. Moreover, in studies testing novel interventions, incomplete assessment of these domains is likely to hinder future therapeutic development. Although this can be challenging in rodents and other small animals, validated methodologies exist and are increasingly accessible to improve our ability to make progress in this field. Recognizing that resource constraints and methodological limitations are real, we offer the following tiered recommendations, ranging from minimum standards applicable to most preclinical OA studies to more comprehensive phenotyping encouraged as therapeutic approaches mature:

- Targeted studies aimed at aimed at defining symptomatic phenotypes and the distinct and inter-related contributions of pain and musculoskeletal function to disability in individual preclinical models are needed.
- Measuring outcomes that capture the domains of *pain, function, and disability* will provide the most complete assessment of disease state and therapeutic efficacy in preclinical models, paralleling the multidimensional nature of human OA with each domain relevant to quality of life and goals of treatment.
- Measuring all three domains in *all* preclinical studies is likely unnecessary, particularly in early-stage studies aimed at defining biological mechanisms of action and molecular targets. However, when designing preclinical studies testing therapeutic efficacy of novel approaches, effort should be made to incorporate outcomes that capture *symptomatic* disease domains in addition to *structural* disease.
- In aging studies, capturing multiple symptom domains is of particular importance due to the differential contribution of age-related comorbidities and muscle loss on pain and function.
- Several behavioral methodologies have emerged to measure OA symptoms in small animal models (reviewed in [31, 32]), and many of these capture multiple symptom domains (pain, function, disability). More work is needed to optimize their use and identify the most suitable/sensitive approaches for specific models before a specific standardized set of outcome measures can be recommended.
- We recommend incorporating at least two outcomes of pain and function, one that measures *spontaneous* pain and function, and one that measures *evoked* pain and function to better capture and define effects of therapeutic interventions[33]. Spontaneous measures capture pain and functional deficits during normal daily activity, paralleling resting pain and functional limitations in "activities of daily living" in our patients. Evoked measures, elicited by a challenge or stressor, capture deficits that emerge under increased stress or physical demands, paralleling activity-related symptoms. Although not an exact proxy for outcomes in patients, these measures together can capture the impact of OA symptoms on the ability of an organism to function. Some examples are as follows:
    - Examples of spontaneous pain and function outcomes include paw weight bearing distribution[23, 34, 35], gait analysis [36-38], and measurement of spontaneous activities (i.e. rearing, climbing, speed of locomotion, voluntary wheel running, exploratory behavior, etc) which can be evaluated using different technologies [39-41].
    - Examples of evoked pain and function include vonFrey filament algesiometry[30], and pressure-application measurement[42], both of which measure nociceptive/pain sensitivity to mechanical stimuli. Functional tests include grip strength measurement [43], forced treadmill running and rotarod testing[44].

- Functional measures may capture multiple symptom domains, and relationship with pain in specific models should be determined by analgesic challenge. Those that capture global motor function (i.e. gait analysis, rotarod testing, spontaneous activity) may represent surrogates for disability.
- Sex-related differences in pain[45] and function[46] outcomes are reported and should be taken into account.
- A recent "comprehensive functional assessment battery (CFAB)" of behavioral tests capture physical function decline with age in mice, and could be useful in age-related OA studies [47].

We recognize that the training of personnel, equipment, and establishing optimal environments for behavioral testing is time-consuming and costly. But **aligning preclinical therapeutic studies to capture clinically relevant outcomes is critical to the development of effective therapies for OA.** Efforts to engage multi-disciplinary teams of investigators to overcome obstacles to rigorous symptomatic phenotyping in preclinical models of OA will be critical towards this goal.

References

1. Hadler NM. Knee pain is the malady--not osteoarthritis. Ann Intern Med. 1992;116(7):598-9. doi: 10.7326/0003-4819-116-7-598. PubMed PMID: 1543316.
2. McDonough CM, Jette AM. The contribution of osteoarthritis to functional limitations and disability. Clin Geriatr Med. 2010;26(3):387-99. doi: 10.1016/j.cger.2010.04.001. PubMed PMID: 20699161; PMCID: PMC3529154.
3. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, Callahan L, Copenhaver C, Dodge C, Felson D, Gellar K, Harvey WF, Hawker G, Herzig E, Kwoh CK, Nelson AE, Samuels J, Scanzello C, White D, Wise B, Altman RD, DiRenzo D, Fontanarosa J, Giradi G, Ishimori M, Misra D, Shah AA, Shmagel AK, Thoma LM, Turgunbaev M, Turner AS, Reston J. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. 2020;72(2):220-33. Epub 20200106. doi: 10.1002/art.41142. PubMed PMID: 31908163; PMCID: PMC10518852.
4. White DK, Neogi T, Nguyen US, Niu J, Zhang Y. Trajectories of functional decline in knee osteoarthritis: the Osteoarthritis Initiative. Rheumatology (Oxford). 2016;55(5):801-8. Epub 20151224. doi: 10.1093/rheumatology/kev419. PubMed PMID: 26705330; PMCID: PMC5009418.
5. van Dijk GM, Veenhof C, Spreeuwenberg P, Coene N, Burger BJ, van Schaardenburg D, van den Ende CH, Lankhorst GJ, Dekker J, Group CS. Prognosis of limitations in activities in osteoarthritis of the hip or knee: a 3-year cohort study. Arch Phys Med Rehabil. 2010;91(1):58-66. doi: 10.1016/j.apmr.2009.08.147. PubMed PMID: 20103397.
6. de Rooij M, van der Leeden M, Heymans MW, Holla JF, Hakkinen A, Lems WF, Roorda LD, Veenhof C, Sanchez-Ramirez DC, de Vet HC, Dekker J. Prognosis of Pain and Physical Functioning in Patients With Knee Osteoarthritis: A Systematic Review and Meta-Analysis. Arthritis Care Res (Hoboken). 2016;68(4):481-92. doi: 10.1002/acr.22693. PubMed PMID: 26316234.
7. Cruz-Almeida Y, Cardoso J, Riley JL, 3rd, Goodin B, King CD, Petrov M, Bartley EJ, Sibille KT, Glover TL, Herbert MS, Bulls HW, Addison A, Staud R, Redden D, Bradley LA, Fillingim RB. Physical performance and movement-evoked pain profiles in community-dwelling individuals at risk for knee osteoarthritis. Exp Gerontol. 2017;98:186-91. Epub 20170824. doi: 10.1016/j.exger.2017.08.026. PubMed PMID: 28842222; PMCID: PMC5652068.
8. Glass NA, Torner JC, Frey Law LA, Wang K, Yang T, Nevitt MC, Felson DT, Lewis CE, Segal NA. The relationship between quadriceps muscle weakness and worsening of knee pain in the MOST cohort: a 5-year longitudinal study. Osteoarthritis Cartilage. 2013;21(9):1154-9. doi: 10.1016/j.joca.2013.05.016. PubMed PMID: 23973125; PMCID: PMC3774035.
9. Hawker GA, Gignac MA, Badley E, Davis AM, French MR, Li Y, Perruccio AV, Power JD, Sale J, Lou W. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. Arthritis Care Res (Hoboken). 2011;63(10):1382-90. Epub 20100726. doi: 10.1002/acr.20298. PubMed PMID: 20662042.
10. Cruz CJ, Tamargo JA, Abbas M, Capote S, Staud R, Goodin BR, Fillingim RB, Cruz-Almeida Y. Hypertension is associated with knee osteoarthritis pain in an age-dependent manner. Exp Gerontol. 2025;212:112938. Epub 20251025. doi: 10.1016/j.exger.2025.112938. PubMed PMID: 41678377.
11. Jacobs CA, Vranceanu AM, Thompson KL, Lattermann C. Rapid Progression of Knee Pain and Osteoarthritis Biomarkers Greatest for Patients with Combined Obesity and Depression: Data from the Osteoarthritis Initiative. Cartilage. 2020;11(1):38-46. Epub 20180601. doi: 10.1177/1947603518777577. PubMed PMID: 29855190; PMCID: PMC6921961.
12. Hertel E, Arendt-Nielsen L, Olesen AE, Andersen MS, Petersen KK. Quantitative sensory testing, psychological factors, and quality of life as predictors of current and future pain in patients with knee osteoarthritis. Pain. 2024;165(8):1719-26. Epub 20240220. doi: 10.1097/j.pain.0000000000003194. PubMed PMID: 38381930.
13. Miller RE, Tran PB, Das R, Ghoreishi-Haack N, Ren D, Miller RJ, Malfait AM. CCR2 chemokine receptor signaling mediates pain in experimental osteoarthritis. Proc Natl Acad Sci U S A. 2012;109(50):20602-7. Epub 20121126. doi: 10.1073/pnas.1209294110. PubMed PMID: 23185004; PMCID: PMC3528555.
14. Chan KM, Griffith JL, Pacheco YC, Allen KD. Wheel Running Exacerbates Joint Damage after Meniscal Injury in Mice, but Does Not Alter Gait or Physical Activity Levels. Med Sci Sports Exerc. 2023;55(9):1564-76. Epub 20230505. doi: 10.1249/MSS.0000000000003198. PubMed PMID: 37144624; PMCID: PMC10524358.
15. Kaiser JM, Bernard FC, Pucha K, Raval SK, Eng T, Fulton T, Anderson SE, Allen KD, Dixon JB, Willett NJ. Mild exercise expedites joint clearance and slows joint degradation in a joint instability model of

osteoarthritis in male rats. Osteoarthritis Cartilage. 2024;32(7):912-21. Epub 20240418. doi: 10.1016/j.joca.2024.03.120. PubMed PMID: 38642879.
16. Miller ME, Rejeski WJ, Messier SP, Loeser RF. Modifiers of change in physical functioning in older adults with knee pain: the Observational Arthritis Study in Seniors (OASIS). Arthritis Rheum. 2001;45(4):331-9. doi: 10.1002/1529-0131(200108)45:4<331::AID-ART345>3.0.CO;2-6. PubMed PMID: 11501720.
17. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord. 2008;9:116. Epub 20080902. doi: 10.1186/1471-2474-9-116. PubMed PMID: 18764949; PMCID: PMC2542996.
18. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol. 2000;27(6):1513-7. PubMed PMID: 10852280.
19. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, Sack B, Torner J, Bradley L, Zhang Y. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. BMJ. 2009;339:b2844. Epub 20090821. doi: 10.1136/bmj.b2844. PubMed PMID: 19700505; PMCID: PMC2730438.
20. Schiphof D, Kerkhof HJ, Damen J, de Klerk BM, Hofman A, Koes BW, van Meurs JB, Bierma-Zeinstra SM. Factors for pain in patients with different grades of knee osteoarthritis. Arthritis Care Res (Hoboken). 2013;65(5):695-702. doi: 10.1002/acr.21886. PubMed PMID: 23203619.
21. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, Campbell CM, Haythornthwaite JA, Edwards RR, Smith MT. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis Rheum. 2013;65(2):363-72. doi: 10.1002/art.34646. PubMed PMID: 22961435; PMCID: PMC3863776.
22. Culvenor AG, Oiestad BE, Hart HF, Stefanik JJ, Guermazi A, Crossley KM. Prevalence of knee osteoarthritis features on magnetic resonance imaging in asymptomatic uninjured adults: a systematic review and meta-analysis. Br J Sports Med. 2019;53(20):1268-78. Epub 20180609. doi: 10.1136/bjsports-2018-099257. PubMed PMID: 29886437; PMCID: PMC6837253.
23. Zaki S, Smith MM, Little CB. Pathology-pain relationships in different osteoarthritis animal model phenotypes: it matters what you measure, when you measure, and how you got there. Osteoarthritis Cartilage. 2021;29(10):1448-61. Epub 20210728. doi: 10.1016/j.joca.2021.03.023. PubMed PMID: 34332049.
24. Kloefkorn HE, Jacobs BY, Loye AM, Allen KD. Spatiotemporal gait compensations following medial collateral ligament and medial meniscus injury in the rat: correlating gait patterns to joint damage. Arthritis Res Ther. 2015;17:287. Epub 20151014. doi: 10.1186/s13075-015-0791-2. PubMed PMID: 26462474; PMCID: PMC4604628.
25. Kloefkorn HE, Jacobs BY, Xie DF, Allen KD. A graphic user interface for the evaluation of knee osteoarthritis (GEKO): an open-source tool for histological grading. Osteoarthritis Cartilage. 2019;27(1):114-7. Epub 20181001. doi: 10.1016/j.joca.2018.09.005. PubMed PMID: 30287396; PMCID: PMC6309770.
26. Longobardi L, Temple JD, Tagliafierro L, Willcockson H, Esposito A, D'Onofrio N, Stein E, Li T, Myers TJ, Ozkan H, Balestrieri ML, Ulici V, Loeser RF, Spagnoli A. Role of the C-C chemokine receptor-2 in a murine model of injury-induced osteoarthritis. Osteoarthritis Cartilage. 2017;25(6):914-25. Epub 20161114. doi: 10.1016/j.joca.2016.11.004. PubMed PMID: 27856294; PMCID: PMC5430000.
27. Bracho-Sanchez E, Rocha FG, Bedingfield SK, Partain BD, Macias SL, Brusko MA, Colazo JM, Fettis MM, Farhadi SA, Helm EY, Koenders K, Kwiatkowski AJ, Restuccia A, Morales BS, Wanchoo A, Avram D, Allen KD, Duvall CL, Wallet SM, Hudalla GA, Keselowsky BG. Suppression of local inflammation via galectin-anchored indoleamine 2,3-dioxygenase. Nat Biomed Eng. 2023;7(9):1156-69. Epub 20230501. doi: 10.1038/s41551-023-01025-1. PubMed PMID: 37127708; PMCID: PMC10504068.
28. Lee KM, Prasad V, Achuthan A, Fleetwood AJ, Hamilton JA, Cook AD. Targeting GM-CSF for collagenase-induced osteoarthritis pain and disease in mice. Osteoarthritis Cartilage. 2020;28(4):486-91. Epub 20200203. doi: 10.1016/j.joca.2020.01.012. PubMed PMID: 32028021.
29. Ismail HM, Miotla-Zarebska J, Troeberg L, Tang X, Stott B, Yamamoto K, Nagase H, Fosang AJ, Vincent TL, Saklatvala J. Brief Report: JNK-2 Controls Aggrecan Degradation in Murine Articular Cartilage and the Development of Experimental Osteoarthritis. Arthritis Rheumatol. 2016;68(5):1165-71. doi: 10.1002/art.39547. PubMed PMID: 26663140.
30. Miller RE, Ishihara S, Tran PB, Golub SB, Last K, Miller RJ, Fosang AJ, Malfait AM. An aggrecan fragment drives osteoarthritis pain through Toll-like receptor 2. JCI Insight. 2018;3(6). Epub 20180322. doi: 10.1172/jci.insight.95704. PubMed PMID: 29563338; PMCID: PMC5926921.

31. Malfait AM, Little CB, McDougall JJ. A commentary on modelling osteoarthritis pain in small animals. Osteoarthritis Cartilage. 2013;21(9):1316-26. doi: 10.1016/j.joca.2013.06.003. PubMed PMID: 23973146; PMCID: PMC3903124.
32. Drevet S, Favier B, Brun E, Gavazzi G, Lardy B. Mouse Models of Osteoarthritis: A Summary of Models and Outcomes Assessment. Comp Med. 2022;72(1):3-13. Epub 20220105. doi: 10.30802/AALAS-CM-21-000043. PubMed PMID: 34986927; PMCID: PMC8915410.
33. Krug HE, Dorman C, Blanshan N, Frizelle S, Mahowald M. Spontaneous and Evoked Measures of Pain in Murine Models of Monoarticular Knee Pain. J Vis Exp. 2019(144). Epub 20190222. doi: 10.3791/59024. PubMed PMID: 30855579; PMCID: PMC7286413.
34. Blanshan N, Mahowald ML, Dorman C, Frizelle S, Krug HE. The analgesic effect of intraarticular OnabotulinumtoxinA in a female murine model of collagenase induced chronic degenerative monoarthritis. Toxicon. 2019;158:8-15. Epub 20181122. doi: 10.1016/j.toxicon.2018.11.307. PubMed PMID: 30471381; PMCID: PMC7291841.
35. Reid AR, Cote PD, McDougall JJ. Long-Term Blockade of Nociceptive Na(v)1.7 Channels Is Analgesic in Rat Models of Knee Arthritis. Biomolecules. 2022;12(11). Epub 20221026. doi: 10.3390/biom12111571. PubMed PMID: 36358921; PMCID: PMC9687684.
36. Savannah Dewberry L, Cruz CJ, Southern KM, Otto KJ, Allen KD. Pipeline Validation for Rodent Gait Analysis Using deeplabcut. J Biomech Eng. 2025;147(11). doi: 10.1115/1.4069390. PubMed PMID: 40802266; PMCID: PMC12617603.
37. Rapp AE, Wolter A, Muschter D, Grassel S, Lang A. Impact of sensory neuropeptide deficiency on behavioral patterns and gait in a murine surgical osteoarthritis model. J Orthop Res. 2024;42(12):2673-82. Epub 20240803. doi: 10.1002/jor.25949. PubMed PMID: 39096166.
38. Makii Y, Asaka M, Setogawa S, Fujiki S, Hosaka Y, Yano F, Oka H, Tanaka S, Fukui N, Yanagihara D, Saito T. Alteration of gait parameters in a mouse model of surgically induced knee osteoarthritis. J Orthop Surg (Hong Kong). 2018;26(2):2309499018768017. doi: 10.1177/2309499018768017. PubMed PMID: 29661110.
39. Burt KG, South SM, Adamczyk NS, Nguyen V, Ishihara S, Zhou C, Sharp KL, Kim SY, Rapp AE, Hu B, Murphy LA, Hung LY, Herbert D, Baker JF, Mauck RL, Griffin TM, Malfait AM, Miller RE, Scanzello CR. CD14 plays a critical role in pain and inflammation across multiple models of post-traumatic osteoarthritis. Arthritis Rheumatol. 2026. Epub 20260224. doi: 10.1002/art.70100. PubMed PMID: 41735778.
40. Ossenkopp KP, Macrae LK, Teskey GC. Automated multivariate measurement of spontaneous motor activity in mice: time course and reliabilities of the behavioral measures. Pharmacol Biochem Behav. 1987;27(3):565-8. doi: 10.1016/0091-3057(87)90368-6. PubMed PMID: 3659081.
41. Roach GC, Edke M, Griffin TM. A novel mouse running wheel that senses individual limb forces: biomechanical validation and in vivo testing. J Appl Physiol (1985). 2012;113(4):627-35. Epub 20120621. doi: 10.1152/japplphysiol.00272.2012. PubMed PMID: 22723628; PMCID: PMC4422345.
42. Ishihara S, Miller RE, Malfait AM. Assessment of Knee Hyperalgesia in Mice using Pressure Application Measurement. J Vis Exp. 2025(220). Epub 20250613. doi: 10.3791/68480. PubMed PMID: 40587399; PMCID: PMC12237626.
43. Zheng Y, Lunn A, Gao J, Chen H, Yao Y. Quantitative evaluation of hindlimb grip strength in mice as a measure of neuromuscular function. MethodsX. 2025;14:103118. Epub 20241225. doi: 10.1016/j.mex.2024.103118. PubMed PMID: 39834676; PMCID: PMC11743548.
44. Ruan MZ, Patel RM, Dawson BC, Jiang MM, Lee BH. Pain, motor and gait assessment of murine osteoarthritis in a cruciate ligament transection model. Osteoarthritis Cartilage. 2013;21(9):1355-64. doi: 10.1016/j.joca.2013.06.016. PubMed PMID: 23973150; PMCID: PMC3757305.
45. Geraghty T, Obeidat AM, Ishihara S, Wood MJ, Li J, Lopes EBP, Scanzello CR, Griffin TM, Malfait AM, Miller RE. Age-Associated Changes in Knee Osteoarthritis, Pain-Related Behaviors, and Dorsal Root Ganglia Immunophenotyping of Male and Female Mice. Arthritis Rheumatol. 2023;75(10):1770-80. Epub 20230714. doi: 10.1002/art.42530. PubMed PMID: 37096632; PMCID: PMC10543384.
46. Janowski AJ, Berardi G, Hayashi K, Plumb AN, Lesnak JB, Khataei T, Martin B, Benson CJ, Sluka KA. The influence of sex on activity in voluntary wheel running, forced treadmill running, and open field testing in mice. Physiol Rep. 2025;13(4):e70246. doi: 10.14814/phy2.70246. PubMed PMID: 39985141; PMCID: PMC11845322.
47. Pajski ML, Maroto R, Byrd C, Graber TG. Longitudinal Decline of Exercise Capacity in Male and Female Mice. J Gerontol A Biol Sci Med Sci. 2025;80(3). doi: 10.1093/gerona/glae293. PubMed PMID: 39693388; PMCID: PMC11809237.