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Reflections from the OARSI 2022 clinical trials symposium: *The pain of OA—Deconstruction of pain and patient-reported outcome measures for the benefit of patients and clinical trial design*

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Authors' Contributions

All authors participated in the CTS, and participated in the discussions leading to the manuscript. M.A. Karsdal (MAK) and V.B. Kraus (VBK) made the first outline of the manuscript. J Tambiah, D Felson, C Ladel, NP Nikolov, D Hodgins (DH), AR Bihlet (ARB), T Neogi, C De Jong, AC Bay-Jensen, R Baron, A Laslop, and A Mobasheri all provided individual expert sections and commented on and modified the draft versions. All of the authors approved the last version of the manuscript.

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Abstract

Objective: Osteoarthritis (OA) drug development is hampered by a number of challenges. One of the main challenges is the apparent discordance between pain and structure, which has had a significant impact on drug development programs and has led to hesitance among stakeholders. Since 2017, the Clinical Trials Symposium (CTS) has been hosted under the Osteoarthritis Research Society International (OARSI) leadership. OARSI and the CTS steering committee yearly invite and encourage discussions on selected special subject matter between regulators, drug developers, clinicians, clinical researchers, biomarker specialists, and basic scientists to progress drug development in the OA field.

Method: The main topic for the 2022 OARSI CTS was to elucidate the many facets of pain in OA and to enable a discussion between regulators (Food and Drug Administration (FDA) and the European Medicines Agency (EMA)) and drug developers to clarify outcomes and study designs for OA drug development.

Results: Signs or symptoms indicative of nociceptive pain occur in 50–70% of OA patients, neuropathic-like pain in 15–30% of patients, and nociplastic pain in 15–50% of patients. Weight-bearing knee pain is associated with bone marrow lesions and effusions. There are currently no simple objective functional tests whose improvements correlate with patient perceptions.

Conclusions: The CTS participants, in collaboration with the FDA and EMA, raised several suggestions that they consider key to future clinical trials in OA including the need for more precise differentiation of pain symptoms and mechanisms, and methods to reduce placebo responses in OA trials.

Keywords

Biomarkers; clinical trial design; FDA; EMA

Introduction

In April 2017, OARSI initiated its Clinical Trials Symposium (CTS) to facilitate discussions between regulators, drug developers, clinicians, clinical researchers, biomarker specialists, and basic scientists to advance OA drug development. The Food and Drug Administration (FDA) considers how a novel treatment would benefit a patient (i.e., how the patient feels and functions). It is essential to demonstrate long-term patient benefits and possibly joint ‘survival’; this may require long-term outcome studies. For sponsors, these studies are associated with considerable risk. These challenges have been addressed annually by the OARSI CTS. For instance, the main topic of the 2021 OARSI CTS was disease activity (1)

and the disease endotype best related to outcomes in OA. A major challenge in the field of OA drug development is the apparent discordance between pain and structure (2). Currently, the understanding of how neurobiological pain mechanisms relate to the OA pain experience and, therefore, how they can be more effectively and safely treated is limited. To address this challenge, the main topic of the 2022 OARSI CTS was to discuss the many facets of pain in OA and to facilitate a discussion between the regulators (FDA and the European Medicines Agency (EMA)) and drug developers to clarify outcomes and study designs for OA drug development. This summary is the opinion of the individual stakeholders of the CTS and not the official opinion of agencies, institutions, or organizations.

Setting the stage: Concordance and discordance between structure and pain

As illustrated by the wide variance in pain in all categories of OA structural severity (Figure 1), patient-reported OA pain is, on a population level, known to be discordant with the radiographic structural severity of the disease (3)(2)(4). However, more sensitive imaging methods for assessing structural disease identify several associations between known structural disease characteristics and pain. For instance, the presence and severity of bone marrow lesions (BMLs) have been associated with pain; similar associations have been reported with synovitis and cartilage lesions (5)(6)(7). Several investigational disease-modifying OA drugs (DMOADs) have been associated with beneficial structural effects, but with no clear concordance between these effects and symptomatic outcomes in the overall study populations (8)(9)(10). The reasons for this are largely unknown, but recent evidence suggests that the pain perception experience in study participants could reduce the ability to report pain specifically related to OA (11)(12). To reduce variability in symptomatic outcome assessments, efforts should be made to reduce the potential for other confounding contributors in clinical trials of OA pain.

Research in sub-categories of pain suggests that weight-bearing pain, compared to non-weight-bearing pain, may better reflect different underlying OA pain mechanisms. Weight-bearing pain is the first pain category to emerge in the development of OA symptoms (13); in contrast to non-weight-bearing pain, weight-bearing pain is associated with BMLs and effusions (14)(15)(16). More research into the etiology of different pain categories is needed to demonstrate how symptomatic outcomes should be used in OA trials.

Intuitively, a reduction in, or even reversal of structural damage, should be associated with beneficial effects manifesting in clinically relevant outcomes. However, the clinical relevance of structural benefits in OA trials has been questioned by recent pharmacological trials with structural but not concurrent symptom benefits (8,9).

Pain is not just pain: Understanding the link between the molecular taxonomy and pain perception

For many years, OA was thought to be the prototype for a nociceptive pain mechanism, i.e., intact nociceptive fibers are activated in the periphery (joint) by degenerative and inflammatory processes. However, recent studies have indicated that a fraction of patients might also be affected by other pain types and underlying mechanisms (17). Neuropathic pain refers to pain due to a nerve lesion. While neuropathy has not been demonstrated

in OA, neuropathic-like pain components can occur if nociceptive fibers in the synovia or fiber sprouts invading the cartilage are damaged. Nociplastic components, as defined by the International Association for the Study of Pain (IASP) (18), are characterized by secondary changes in nociceptive processing in the spinal cord, i.e., central sensitization. These components can also occur in combination (Figure 2). Easy-to-use assessment tools (questionnaires and bedside tests) are available to phenotype OA patients according to these underlying pain mechanisms (19)(20)(21). The use of these tools revealed that signs or symptoms indicative of nociceptive pain occur in 50–70% of patients, neuropathic-like pain in 15–30% of patients, and nociplastic pain in 15–50% of patients (19)(20)(21). Treatment for neuropathic pain (with damage to the somatosensory system), and nociplastic pain (with central sensitization), differs markedly from treatment for nociceptive pain. Thus, the more precise differentiation of the pain symptoms and mechanisms make an important contribution to successful treatment.

The illness of osteoarthritis and illness versus disease

Illness is not the same as disease, or disease activity (22)(23). ‘Disease’ refers to abnormalities of the structure (24) and has specific molecular and clinical characteristics. ’Illness’ refers to the human experience of disease (24), such as ‘what the patient feels when he goes to the doctor’ (24). When molecular components of the disease and associated disease activity drive patients beyond the illness threshold they experience the symptomatic phase, as described in (23) and (25). Illness of OA is characterized by symptoms such as pain, aching, stiffness, and functional limitations. The pain experience is multidimensional and typically changes over time at differing rates in individuals with knee OA. Initially, the pain is primarily weight-bearing activity-related, increasing in severity over time with pain fluctuations, and becoming more persistent, even occurring at rest for some, and punctuated by episodes of increased pain that may be triggered or unpredictable (26).

Examining the ‘disease’ (structure), at least based on an insensitive measure such as a radiograph, does not explain the ‘illness’ (symptoms). The reason for this discrepancy is related in part to the insensitivity of the structural measure and, importantly, to the multifactorial nature of pain. Structural pathology is not the sole contributor to the pain experience; thus, without accounting for the other factors that influence the pain experience, such as psychological factors, sociocultural context, genetics, etc., the specific impact of joint pathology on joint pain is difficult to discern (27).

Figure 3 illustrates four hypothetical study participants. If a treatment targets an OA pathologic feature that is expected to result in improved nociception, then participants such as Persons 3 and 4 would be preferred for trial enrollment to optimize the ability to detect pain improvement due to that pain mechanism being specifically targeted. However, one would not expect much of a pain benefit for Persons 1 or 2 with such an intervention, since OA nociception contributes only a small proportion to their overall pain experience.

Disease activity may change biologically, i.e., different components of the total joint pathophysiology may contribute differently to the overall pain burden and experience. Consequently, a challenge in OA trials is understanding when to intervene and how to target treatments. Just as there is a perceived structure–symptom discordance due to numerous

factors contributing to the pain experience, there is also a recognized discordance between disease activity and radiographic disease status, with long periods of inertia followed by fast progression (28). We have begun to appreciate that OA has multiple drivers of disease, most likely at different stages of disease (29)(23); in Figure 4 depicts a mechanism-based approach to identifying the driver of disease activity to enable matching of therapeutics to the intervention's mechanism of action. Although better symptom modifiers are in themselves worthy of investigation, solely treating the symptoms, i.e., the illness (pain), may not correct the underlying disease processes that will continue to contribute to symptoms if left unaddressed.

BIOCHEMICAL MARKERS—BIOMARKERS OF DISEASE ACTIVITY

Biochemical markers may play a key role in understanding disease activity, as they reflect the molecular changes that drive or are a consequence of disease. There are quite a few examples of this in the literature (30). For instance, disease activity may be related to either high or low levels of cellular activity, which could, for example, be an assessment of high or low levels of cartilage degradation or formation. Notably, recent data suggest that OA is not just a disease of cartilage loss, but also a disease of low capacity for cartilage repair, e.g., low cartilage formation (31)(32)(33). In the FORWARD trial, patients with low cartilage formation, measured by low serum levels of PRO-C2, responded significantly better to the chondro-anabolic drug FGF-18 (sprifermin) (9). Moreover, PRO-C2 predicted structural knee OA progression (34). Similarly, low serum levels of the anabolic biomarker PIIANP were predictive of two-year progression in the FNIH study. This supposition is also supported by the UK Biobank resource which in a case control study showed that patients with specific single nucleotide polymorphisms associated to cartilage repair and cartilage formation were more likely to have incident OA.(35). Other biomarkers are worth additional attention (36)(31)(37)(38)(39)(40) but are beyond the scope of the current discussion.

Considerations for osteoarthritis drug development from progress in Alzheimer's disease

To optimize effectiveness of DMOADs, earlier intervention is needed; early intervention requires a better understanding of the pathogenesis of OA (41)(42)(43). However, during these early stages, a patient with OA may not experience 'illness'; thus, identifying such patients for participation in clinical trials has proven to be problematic due to a lack of biomarkers with which to predict risk and diagnose early/pre-symptomatic OA. The following is a brief discussion of how similar challenges, faced by researchers in Alzheimer's disease (AD), have been approached and tackled.

From a drug development perspective, AD provides a parallel case study to knee OA, as it is another chronic degenerative disease with an unclear and heterogeneous pathology. AD researchers have similarly recognized that earlier intervention is required to develop successful disease-modifying treatments. A hallmark of AD, β-amyloid (designated 'A'), is present in plaques even before symptomatic disease. Phosphorylated tau (designated 'T') is also an AD hallmark and is found in neurofibrillary tangles as a marker of disease progression. Finally, total tau (designated 'N') is a non-specific marker of neurodegeneration (44). The AD signature biomarker profile is always A positive but can be positive or

negative for T and/or N. Subsequently, combining A, T, and N biomarker status with cognitive impairment symptoms has enabled researchers to deconstruct dementia into several clinical syndromes, of which AD is one (Fig. 4) (45)(46). This concept has been incorporated into the recent National Institute on Aging and Alzheimer's Association (NIA-AA) 2018 AD classification criteria (Table 1), which has allowed greater flexibility in trial design, as trial participant specificity can be adjusted by different ATN combinations. This classification system has also enhanced the recruitment of early- and pre-symptomatic participants. Post-trial ATN biomarker combinations can be used to retrospectively probe participant profiles and identify subgroups of interest, for example, to characterize test-drug responders. When new biomarkers are discovered, the ATN nomenclature remains versatile, as another letter designation can easily be added. It is important to note, however, that this classification framework is designed for research use only (i.e., for defining homogenous clinical research cohorts) and not for any clinical purpose.

As a demonstration of effectiveness, in a recent trial, the ATN criteria proved more discriminatory of drug effect than the clinical symptoms (47). Another application of this biological approach is the recent FDA conditional approval of aducanumab (a monoclonal antibody that binds directly to amyloid beta plaques, facilitating their removal by host immune mechanisms) to treat patients with AD under its Accelerated Approval Program (48). The FDA's stance regarding these data was that amyloid plaque levels represent a surrogate biomarker of cognitive decline and that their reduction predicts clinical benefits. Note that to gain full approval under the Accelerated Approval Program, the sponsor must still provide further phase 4 trial evidence confirming clinically relevant effects.

For AD, the identification of β-amyloid as a pre-symptomatic pathognomonic structural hallmark of disease created the ability to develop biological classification criteria for pre-symptomatic subjects and, therefore, possibilities for drug intervention before cognitive decline. At present, as no such hallmarks have been validated for OA, moving to a biological classification framework is currently not possible. However, much research is ongoing to develop pre-radiographic detection of OA using MRI, other specialized imaging, deep learning techniques, and molecular biomarkers (49)(50)(51). If any become validated as risk, diagnostic, or predictive OA biomarkers (as defined by the FDA-NIH Biomarker Working Group) (52), these will facilitate the development of OA classification systems, research-focused biological disease frameworks, and new means of patient targeting. Considering disease diagnosis, AD is now known to be a subset of dementias, whereas knee OA remains a 'catch-all' diagnosis. It is still not clear whether OA is a single disease or many diseases; thus, more research is needed on early OA and OA phenotypes.

Optimizing the assessment of pain and structural outcomes in osteoarthritis clinical studies

Improving the sensitivity of pain assessment in OA clinical trials might more readily reveal the efficacy of treatments. Some evidence suggests that WOMAC and KOOS are less sensitive to change than a global knee pain question, suggesting that the latter may be preferred in trials (53)(54). Other approaches to pain surveys may have an even greater sensitivity to change, including composite measures (55), patient preference measures, and

even asking the patient to carry out an activity that is likely to induce pain and then assess pain severity (56).

The placebo response in clinical trials has compromised our ability to detect treatment-placebo differences (57). One approach might be to minimize possible responses by (1) lowering expectations about treatment, (2) excluding persons whose pain scores vary greatly from day to day, and (3) training potential participants to accurately score pain stimuli or use a secondary outcome could be staircase-evoked pain using a recently validated protocol (58).. For instance, the trial could include a script with recruitment that does not promise that the patient's pain will improve (minimizing expectation and thereby placebo response),.

Consistent relationships exist between OA symptoms and select structural features, including large BMLs, synovitis and effusion, and cartilage volume/thickness (59). Cartilage remains the primary structural outcome targeted by therapeutic agents, but it is only one of many pathologic features of OA, as OA is a disease of the whole joint organ. Healthy cartilage has no pain fibers, and the correlation between cartilage loss and pain reduction is weak. This underlies the failure of much drug development in OA. Other structures, also part of the pathologic process of OA, are innervated by nociceptors, and their changes are associated with both pain change and cartilage loss. These structures, including BMLs, synovitis, and bone shape, are likely to be more responsive to therapeutic agents and to correlate better with pain change than treatments targeting cartilage (60)(61)(62), although we need efficacious treatment to affect these structures.

The design of future OA trials should also focus on reducing the problem of regression to the mean(63). In addition to specific statistical approaches, researchers can take multiple baseline measurements to select participants based on the average of their multiple measurements, not just on a single test. Control of this issue is best achieved during the design stage by conducting a RCT.

Should we consider other pain-associated features, such as gait?

Given the importance of function, it is essential to consider whether objective function or patient-perceived function will be used as outcome measures or whether it is necessary to identify a new objective functional outcomes that correlates with the PROs. Changes in gait, quality, and quantity may be the ultimate outcome prior to total joint replacement (TJR). Gait is a patient-specific measure that may be quantified more objectively and robustly than TJRs. As stated by the FDA and EMA, any drug approved for use must have a positive effect on how a patient feels or functions and must be interpretable with respect to the expected clinical benefit. Two recent studies (64)(65) have highlighted weak correlation and poor construct validity between PRO measures and the commonly used functional tests: 6 minute walk test, 40 m walk test, timed up and go (TUG) test, and stair climb. The MOST study (66) evaluated whether patients with clinically meaningful worsening knee pain at two years, defined as ≥20% rise in WOMAC pain, walked fewer steps. The presence of radiographic OA and consistent frequent knee pain at baseline and the clinically meaningful worsening of knee pain over two years were not associated with a meaningful decline in walking. These findings suggest that simple step count and patient-reported pain worsening are discordant. Longitudinal data over six months in the IMI APPROACH project

(67) showed that certain gait kinematic parameters were related to subjective function, a PROM, while others were related to objective function. In summary, there are no simple objective functional tests whose improvements correlate with patient perceptions. Some evidence shows that gait kinematic data may help bridge the gap between subjective and objective functions. However, these measurements are not currently accepted as primary outcome measures, despite offering a relatively objective quantifiable measure of function. Nevertheless, it is hoped that this situation will change as more evidence is gathered to confirm how they relate to how a person feels, including their pain, and these data are presented to regulatory bodies.

Reflections on the regulatory considerations related to biomarkers and assessment of long-term benefits in OA from the FDA

The basis of the FDA's regulatory decision-making is weighing the clinical benefit, which is generally defined by an improvement in how a patient feels, functions, or survives, versus the potential or known risks of a product. In that framework, every product is expected to show clinical benefits. Respectively, endpoints in trials of OA treatments are also expected to demonstrate clinical benefit or, at least, be interpretable with respect to the expected clinical benefit.

The FDA considers many outcome measures in a clinical program, and each measure addresses different questions in drug development. For example, clinical efficacy endpoints that measure how a patient feels, functions, or survives are used in clinical programs supporting traditional approval, while surrogate endpoints are expected to predict clinical benefit, or harm, and can be used in certain situations to support an accelerated approval. Biomarkers, on the other hand, are objective measures of a normal biologic process, a pathogenic process, or a pharmacologic response to an intervention that may be helpful in early clinical development to identify therapeutic targets, the biological activity of a product, and/or appropriate doses, etc.

Using PRO measures that assess reduction in pain, patient global assessment, and/or improving function in short clinical trials has successfully supported the traditional approval of symptomatic treatments for OA. However, due to the complex etiopathogenesis of OA and its slow progression, the clinical benefits related to changes in biomarkers, such as common measures of structural progression or biochemical markers, remain elusive to capture and represent an unmet medical need. Thus, defining the clinical benefit(s) of therapies intended to alter the natural history of OA is critical for expediting the development of such therapies. Specifically, to use structural/biochemical markers in the benefit-risk assessment of a product, one needs to be able to describe the clinical benefit expected from the biomarker change; this means that a high level of characterization is needed regarding the relationship of the endpoint to the anticipated defined clinical benefit.

To help address this knowledge gap, based on analyses of Osteoarthritis Initiative (OAI) data, reviewers at the FDA proposed a conceptual approach with a composite endpoint using total knee replacement rates and unacceptable levels of pain and disability to define severe disease (68). Therefore, demonstrating a delay in the development of severe disease would be a clinically meaningful long-term benefit of a product intended to change the

disease course in OA and could provide key evidence on the much-needed understanding of how a biomarker change can predict that clinical benefit. This approach can be further complemented by employing enrichment strategies, studies in models of accelerated OA, and innovative trial designs. The FDA recognizes the important public health need in OA and is open to collaborating with all stakeholders to bring safe and effective treatments for OA to market.

Reflections on the osteoarthritis drug development landscape of EMA

Even though its latest update was in 2010, the EMA guideline on OA (CPMP/EWP/784/97 Rev. 1) can, in many respects, still be seen as relevant guidance for the development of new drugs to treat OA. It currently distinguishes between drugs that provide fast symptom relief for the treatment of acute flares, symptom-modifying slow-acting drugs, and disease-modifying drugs that show properties impacting the structural progression of the disease. Separate considerations are given for symptom- and disease-modifying medicinal products in terms of primary and secondary endpoints as well as the instruments being used to measure these endpoints. For pain, a patient elicited measurement on a continuous visual analog scale is preferred over a numerical rating scale, which, however, may also be acceptable. A study participant's function should ideally be captured as a co-primary endpoint, using validated disease- and joint-specific instruments.

Clinical endpoints, such as the need for joint replacement, time to the need for virtual or actual surgery, and long-term clinical evolution (of pain and disability), are favored for the assessment of drugs with the potential to slow disease progression. However, as an alternative, the measurement of radiographic joint space narrowing, which is shown to correlate with the need for TJR, may also be accepted as a primary endpoint. In this case, a clinically relevant effect needs to be pre-determined, and an evaluation of improvement in pain and function should be incorporated to support the surrogacy value of radiographic changes. Both MRI as a method of quantification of cartilage and various biomarkers as predictors of progression and response to treatment require further validation.

In general, relatively few development programs aimed at the treatment of OA have been seen over the past few years. With the hope of more activity emerging in the field, it will be important to revise the EMA guidance on OA. Such a revision may give a clear outline of intended therapeutic claims, such as improvement of symptoms and functional disability, slowing of the disease course, or prevention of structural damage; it may further specify definitions and use of clinical and imaging endpoints and include new clinical trial design considerations.

To envisage alternative study designs, parallels could be drawn with new insights gained in OA and type 1 diabetes mellitus, both of which have been recognized as multifactorial and heterogeneous diseases that may be subdivided into different molecular endotypes. Different molecular endotypes could merit stratification in clinical trials, with potential enrichment designs and the selection of relevant outcome measures. Another approach could be to consider delayed-start designs, taking into account the often slowly progressive disease course, where the benefit of early intervention may be observed over extended treatment periods to confirm the improvement of the long-term structural outcome. These

two scenarios might be seen as part of a wider research agenda for clinical trial designs that could facilitate the identification of new safe and efficacious treatments for OA. The importance of including PROs to reflect the patient's perspective on the disease and treatments received is recognized by the EMA and will be further strengthened in the future.

Conclusion

In conclusion, although many challenges remain in OA drug development, a more nuanced understanding of OA pain, its heterogeneity, and the means of relating it to structural modification is expected to advance the field of OA therapeutics. The OA research community—academic and industry—brought together through regulatory agency representatives under the OARSI banner are optimistic that these developments and continual close collaboration will result in meaningful improvements in options for providing substantive clinically meaningful therapies for OA in the not-too-distant future.

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References

1. Karsdal MA, Tambiah J, Hochberg MC, Ladel C, Bay-Jensen AC, Arendt-Nielsen L, et al. Reflections from the 2021 OARSI clinical trial symposium: Considerations for understanding biomarker assessments in osteoarthritis drug development - Should future studies focus on disease activity, rather than status? Osteoarthr Cartil Open [Internet]. 2022 Sep;4(3):100262. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2665913122000309 [PubMed: 36474940]
2. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord [Internet]. 2008 Sep 2;9:116. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18764949 [PubMed: 18764949]
3. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol [Internet]. 2000 Jun;27(6):1513–7.Available from: http://www.ncbi.nlm.nih.gov/pubmed/10852280 [PubMed: 10852280]
4. Barr AJ, Campbell TM, Hopkinson D, Kingsbury SR, Bowes MA, Conaghan PG. A systematic review of the relationship between subchondral bone features, pain and structural pathology in peripheral joint osteoarthritis. Arthritis Res Ther [Internet]. 2015 Aug 25;17:228. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26303219 [PubMed: 26303219]
5. Hill CL, Gale DR, Chaisson CE, Skinner K, Kazis L, Gale ME, et al. Periarticular lesions detected on magnetic resonance imaging: prevalence in knees with and without symptoms. Arthritis Rheum [Internet]. 2003 Oct;48(10):2836–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14558089 [PubMed: 14558089]
6. Hill CL, Gale DG, Chaisson CE, Skinner K, Kazis L, Gale ME, et al. Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis. J Rheumatol [Internet]. 2001 Jun;28(6):1330–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11409127 [PubMed: 11409127]
7. Sayre EC, Guermazi A, Esdaile JM, Kopec JA, Singer J, Thorne A, et al. . Associations between MRI features versus knee pain severity and progression: Data from the Vancouver Longitudinal Study of Early Knee Osteoarthritis. PLoS One [Internet]. 2017;12(5):e0176833. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28472071 [PubMed: 28472071]

8. Conaghan PG, Bowes MA, Kingsbury SR, Brett A, Guillard G, Rizoska B, et al. Disease-Modifying Effects of a Novel Cathepsin K Inhibitor in Osteoarthritis: A Randomized Controlled Trial. Ann Intern Med [Internet]. 2020;172(2):86–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31887743 [PubMed: 31887743]

9. Hochberg MC, Guermazi A, Guehring H, Aydemir A, Wax S, Fleuranceau-Morel P, et al. Effect of Intra-Articular Sprifermin vs Placebo on Femorotibial Joint Cartilage Thickness in Patients With Osteoarthritis. JAMA. 2019 Oct;322(14):1360. [PubMed: 31593273]

10. Reginster J-Y, Badurski J, Bellamy N, Bensen W, Chapurlat R, Chevalier X, et al. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. Ann Rheum Dis [Internet].2013 Feb;72(2):179–86.Availablefrom: http://www.ncbi.nlm.nih.gov/pubmed/23117245 [PubMed: 23117245]

11. Bihlet AR, Byrjalsen I, Andersen JR, Öberg F, Herder C, Bowes MA, et al. Symptomatic and structural benefit of cathepsin K inhibition by MIV-711 in a subgroup with unilateral pain: post-hoc analysis of a randomised phase 2a clinical trial. Clin Exp Rheumatol [Internet]. 2022 May;40(5):1034–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/35238765 [PubMed: 35238765]

12. Yazici Y, McAlindon TE, Gibofsky A, Lane NE, Clauw D, Jones M, et al. Lorecivivint, a Novel Intraarticular CDC-like Kinase 2 and Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase 1A Inhibitor and Wnt Pathway Modulator for the Treatment of Knee Osteoarthritis: A Phase II Randomized Trial. Arthritis Rheumatol (Hoboken, NJ) [Internet]. 2020;72(10):1694–706. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32432388

13. Hensor EMA, Dube B, Kingsbury SR, Tennant A, Conaghan PG. Toward a clinical definition of early osteoarthritis: onset of patient-reported knee pain begins on stairs. Data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) [Internet]. 2015 Jan;67(1):40–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25074673 [PubMed: 25074673]

14. Aso K, Shahtaheri SM, McWilliams DF, Walsh DA. Association of subchondral bone marrow lesion localization with weight-bearing pain in people with knee osteoarthritis: data from the Osteoarthritis Initiative. Arthritis Res Ther [Internet]. 2021;23(1):35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33468243 [PubMed: 33468243]

15. Lo GH, McAlindon TE, Niu J, Zhang Y, Beals C, Dabrowski C, et al. Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthr Cartil [Internet]. 2009 Dec;17(12):1562–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19583959

16. Karsdal MA, Bay-Jensen AC, Lories RJ, Abramson S, Spector T, Pastoureau P, et al. The coupling of bone and cartilage turnover in osteoarthritis: Opportunities for bone antiresorptives and anabolics as potential treatments? Ann Rheum Dis. 2014;73(2).

17. Thakur M, Dickenson AH, Baron R. Osteoarthritis pain: nociceptive or neuropathic? Nat Rev Rheumatol [Internet]. 2014;10(6):374–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24686507 [PubMed: 24686507]

18. Nijs J, Lahousse A, Kapreli E, Bilika P, Saraçoğlu İ, Malfliet A, et al. Nociplastic Pain Criteria or Recognition of Central Sensitization? Pain Phenotyping in the Past, Present and Future. J Clin Med [Internet]. 2021 Jul 21;10(15). Available from: http://www.ncbi.nlm.nih.gov/pubmed/34361986

19. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin [Internet]. 2006 Oct;22(10):1911–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17022849 [PubMed: 17022849]

20. Tölle TR, Baron R, de Bock E, Junor R, Dias Barbosa C, Marshall SF, et al. painPREDICT: first interim data from the development of a new patient-reported pain questionnaire to predict treatment response using sensory symptom profiles. Curr Med Res Opin [Internet]. 2019;35(7):1177–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30572741 [PubMed: 30572741]

21. Sachau J, Otto JC, Kirchhofer V, Larsen JB, Kennes LN, Hüllemann P, et al. . Development of a bedside tool-kit for assessing sensitization in patients with chronic osteoarthritis knee pain or

chronic knee pain after total knee replacement. Pain [Internet]. 2022;163(2):308–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33990109 [PubMed: 33990109]

22. Kraus VB, Simon LS, Katz JN, Neogi T, Hunter D, Guermazi A, et al. Proposed study designs for approval based on a surrogate endpoint and a post-marketing confirmatory study under FDA's accelerated approval regulations for disease modifying osteoarthritis drugs. Osteoarthr Cartil [Internet]. 2019 Apr;27(4):571–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30465809
23. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. Osteoarthr Cartil. 2015;23(8).
24. Helman CG. Disease versus illness in general practice. J R Coll Gen Pract. 1981 Sep;31(230):548–52.
25. Karsdal MA, Genovese F, Rasmussen DGK, Bay-Jensen AC, Mortensen JH, Holm Nielsen S, et al. Considerations for understanding protein measurements: Identification of formation, degradation and more pathological relevant epitopes. Clin Biochem [Internet]. 2021 Nov;97:11–24. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0009912021002289 [PubMed: 34453894]
26. Hawker GA, Davis AM, French MR, Cibere J, Jordan JM, March L, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. Osteoarthr Cartil [Internet]. 2008 Apr;16(4):409–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18381179
27. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthr Cartil [Internet]. 2013 Sep;21(9):1145–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23973124
28. Felson D, Niu J, Sack B, Aliabadi P, McCullough C, Nevitt MC. Progression of osteoarthritis as a state of inertia. Ann Rheum Dis [Internet]. 2013 Jun;72(6):924–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22753401 [PubMed: 22753401]
29. Karsdal MA, Christiansen C, Ladel C, Henriksen K, Kraus VB, Bay-Jensen AC. Osteoarthritis--a case for personalized health care? Osteoarthr Cartil. 2014 Jan;22(1):7–16.
30. Karsdal MA, Henriksen K, Bay-Jensen AC. Biochemical markers in osteoarthritis with lessons learned from osteoporosis. Clin Exp Rheumatol. 2019;37(5).
31. Angelini F, Widera P, Mobasheri A, Blair J, Struglics A, Uebelhoer M, et al. Osteoarthritis endotype discovery via clustering of biochemical marker data. Ann Rheum Dis [Internet]. 2022 Mar 4; Available from: http://www.ncbi.nlm.nih.gov/pubmed/35246457
32. Kraus VB, Collins JE, Hargrove D, Losina E, Nevitt M, Katz JN, et al. Predictive validity of biochemical biomarkers in knee osteoarthritis: data from the FNIH OA Biomarkers Consortium. Vol. 76, Ann.Rheum.Dis. p. 186–95. [PubMed: 27296323]
33. Bay-Jensen AC, Manginelli AA, Karsdal M, Luo Y, He Y, Michaelis M, et al. Low levels of type II collagen formation (PRO-C2) are associated with response to sprifermin: a pre-defined, exploratory biomarker analysis from the FORWARD study. Osteoarthr Cartil [Internet]. 2022 Jan;30(1):92–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34737064
34. Luo Y, Samuels J, Krasnokutsky S, Byrjalsen I, Kraus VB, He Y, et al. A low cartilage formation and repair endotype predicts radiographic progression of symptomatic knee osteoarthritis. J Orthop Traumatol. 2021 Dec;22(1).
35. Tachmazidou I, Hatzikotoulas K, Southam L, Esparza-Gordillo J, Haberland V, Zheng J, et al. Identification of new therapeutic targets for osteoarthritis through genome-wide analyses of UK Biobank data. Nat Genet [Internet]. 2019;51(2):230–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30664745 [PubMed: 30664745]
36. Hunter DJ, Collins JE, Deveza L, Hoffmann SC, Kraus VB. Biomarkers in osteoarthritis: current status and outlook - the FNIH Biomarkers Consortium PROGRESS OA study. Skeletal Radiol [Internet]. 2023 Jan 24; Available from: http://www.ncbi.nlm.nih.gov/pubmed/36692532
37. Bay-Jensen AC, Mobasheri A, Thudium CS, Kraus VB, Karsdal MA. Blood and urine biomarkers in osteoarthritis - an update on cartilage associated type II collagen and aggrecan markers. Curr Opin Rheumatol [Internet]. 2022 Jan 1;34(1):54–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34652292 [PubMed: 34652292]

38. Kraus VB, Karsdal MA. Clinical monitoring in osteoarthritis: Biomarkers. Osteoarthr Cartil [Internet]. 2022 Sep;30(9):1159–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34536529
39. Henkel C, Styrkársdóttir U, Thorleifsson G, Stefánsdóttir L, Björnsdóttir G, Banasik K, et al. Genome-wide association meta-analysis of knee and hip osteoarthritis uncovers genetic differences between patients treated with joint replacement and patients without joint replacement. Ann Rheum Dis [Internet]. 2022 Nov 14; Available from: http://www.ncbi.nlm.nih.gov/pubmed/36376028
40. Styrkarsdottir U, Lund SH, Thorleifsson G, Saevarsdottir S, Gudbjartsson DF, Thorsteinsdottir U, et al. Cartilage Acidic Protein 1 in Plasma Associates With Prevalent Osteoarthritis and Predicts Future Risk as Well as Progression to Joint Replacements: Results From the UK Biobank Resource. Arthritis Rheumatol (Hoboken, NJ) [Internet]. 2022 Oct 14; Available from: http://www.ncbi.nlm.nih.gov/pubmed/36239377
41. Im G-I. The Concept of Early Osteoarthritis and Its Significance in Regenerative Medicine. Tissue Eng Regen Med [Internet]. 2022 Jun 4;19(3):431–6. Available from: https://link.springer.com/10.1007/s13770-022-00436-6 [PubMed: 35244885]
42. Emery CA, Whittaker JL, Mahmoudian A, Lohmander LS, Roos EM, Bennell KL, et al. Establishing outcome measures in early knee osteoarthritis. Nat Rev Rheumatol [Internet]. 2019;15(7):438–48. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31201386 [PubMed: 31201386]
43. Mahmoudian A, Lohmander LS, Mobasheri A, Englund M, Luyten FP. Early-stage symptomatic osteoarthritis of the knee - time for action. Nat Rev Rheumatol [Internet]. 2021;17(10):621–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34465902 [PubMed: 34465902]
44. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. J Intern Med [Internet]. 2018 Dec;284(6):643–63. Available from: https://onlinelibrary.wiley.com/doi/10.1111/joim.12816 [PubMed: 30051512]
45. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. . The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement [Internet]. 2011 May 22;7(3):263–9. Available from: https://onlinelibrary.wiley.com/doi/10.1016/j.jalz.2011.03.005 [PubMed: 21514250]
46. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement [Internet]. 2018 Apr;14(4):535–62. Available from: https://onlinelibrary.wiley.com/doi/10.1016/j.jalz.2018.02.018 [PubMed: 29653606]
47. Allegri RF, Chrem Méndez P, Calandri I, Cohen G, Martín ME, Russo MJ, et al. Prognostic value of ATN Alzheimer biomarkers: 60-month follow-up results from the Argentine Alzheimer's Disease Neuroimaging Initiative. Alzheimer's Dement Diagnosis, Assess Dis Monit [Internet]. 2020 Jan 22;12(1). Available from: https://onlinelibrary.wiley.com/doi/10.1002/dad2.12026
48. Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimer's Dis [Internet]. 2022; Available from: https://link.springer.com/article/10.14283/jpad.2022.30
49. Lee JJ, Namiri NK, Astuto B, Link TM, Majumdar S, Pedoia V. A Personalized Risk Model Leverages <scp>MRI</scp> -based Structural Phenotypes and Clinical Factors to Predict Incidence of Radiographic Osteoarthritis. Arthritis Care Res (Hoboken) [Internet]. 2022 Mar 4; Available from: https://onlinelibrary.wiley.com/doi/10.1002/acr.24877
50. Mohajer B, Eng J, Roemer FW, Guermazi A, Demehri S. DEEP-LEARNING ASSESSED BONE MARROW LESIONS CAN PREDICT FUTURE RADIOGRAPHIC OSTEOARTHRITIS INCIDENCE AND SYMPTOM WORSENING: OAI DATA. Osteoarthr Imaging [Internet]. 2022;2:100055. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2772654122000496
51. Valdes AM, Meulenbelt I, Chassaing E, Arden NK, Bierma-Zeinstra S, Hart D, et al. Large scale meta-analysis of urinary C-terminal telopeptide, serum cartilage oligomeric protein and matrix metalloprotease degraded type II collagen and their role in prevalence, incidence and progression of osteoarthritis. Osteoarthr Cartil [Internet]. 2014 May;22(5):683–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24576742

52. Group F-NBW. BEST (Biomarkers, EndpointS, and other Tools) Resource. BEST (Biomarkers, EndpointS, and other Tools) Resource. Food and Drug Administration (US); 2016.
53. da Costa BR, Saadat P, Basciani R, Agarwal A, Johnston BC, Jüni P. Visual Analogue Scale has higher assay sensitivity than WOMAC pain in detecting between-group differences in treatment effects: a meta-epidemiological study. Osteoarthr Cartil [Internet]. 2021 Mar;29(3):304–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33271331
54. Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain [Internet]. 2009 Dec;146(3):238–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19836888 [PubMed: 19836888]
55. Parkes MJ, Callaghan MJ, O'Neill TW, Forsythe LM, Lunt M, Felson DT. Sensitivity to Change of Patient-Preference Measures for Pain in Patients With Knee Osteoarthritis: Data From Two Trials. Arthritis Care Res (Hoboken) [Internet]. 2016 Sep;68(9):1224–31. Available from: https://onlinelibrary.wiley.com/doi/10.1002/acr.22823 [PubMed: 26713415]
56. Treister R, Suzan E, Lawal OD, Katz NP. Staircase-evoked Pain May be More Sensitive Than Traditional Pain Assessments in Discriminating Analgesic Effects: A Randomized, Placebo-controlled Trial of Naproxen in Patients With Osteoarthritis of the Knee. Clin J Pain [Internet]. 2019 Jan;35(1):50–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30222614 [PubMed: 30222614]
57. Tuttle AH, Tohyama S, Ramsay T, Kimmelman J, Schweinhardt P, Bennett GJ, et al. Increasing placebo responses over time in U.S. clinical trials of neuropathic pain. Pain [Internet]. 2015 Dec;156(12):2616–26. Available from: https://journals.lww.com/00006396-201512000-00027 [PubMed: 26307858]
58. Treister R, Suzan E, Lawal OD, Katz NP. Staircase-evoked Pain May be More Sensitive Than Traditional Pain Assessments in Discriminating Analgesic Effects. Clin J Pain [Internet]. 2019 Jan;35(1):50–5. Available from: https://journals.lww.com/00002508-201901000-00008 [PubMed: 30222614]
59. Hunter DJ, Guermazi A, Roemer F, Zhang Y, Neogi T. Structural correlates of pain in joints with osteoarthritis. Osteoarthr Cartil [Internet]. 2013 Sep;21(9):1170–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23973127
60. Bacon K, LaValley MP, Jafarzadeh SR, Felson D. Response to: "Relation between cartilage loss and pain in knee osteoarthritis" by Wu et al and "Changes in synovitis and bone marrow lesions may not mediate the effect of cartilage loss on joint pain in osteoarthritis" by Cashin et al. Ann Rheum Dis [Internet]. 2020 Oct 7; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33028581
61. Callaghan MJ, Parkes MJ, Hutchinson CE, Gait AD, Forsythe LM, Marjanovic EJ, et al. A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. Ann Rheum Dis [Internet]. 2015 Jun;74(6):1164–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25596158 [PubMed: 25596158]
62. O'Neill TW, Parkes MJ, Maricar N, Marjanovic EJ, Hodgson R, Gait AD, et al. Synovial tissue volume: a treatment target in knee osteoarthritis (OA). Ann Rheum Dis [Internet]. 2016 Jan;75(1):84–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26116548 [PubMed: 26116548]
63. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol [Internet]. 2005 Feb;34(1):215–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15333621 [PubMed: 15333621]
64. Onodera CMK, Coelho-Júnior HJ, Sampaio RAC, Santos Duarte Lana JF, Teixeira LFM, Uchida MC, et al. The importance of objectively measuring functional tests in complement to self-report assessments in patients with knee osteoarthritis. Gait Posture [Internet].2020;82:33–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32871410 [PubMed: 32871410]
65. Tolk JJ, Janssen RPA, Prinsen CAC, Latijnhouwers DAJM, van der Steen MC, Bierma-Zeinstra SMA, et al. The OARSI core set of performance-based measures for knee osteoarthritis is reliable but not valid and responsive. Knee Surgery, Sport Traumatol Arthrosc [Internet]. 2019 Sep 11;27(9):2898–909. Available from: http://link.springer.com/10.1007/s00167-017-4789-y

66. White DK, Tudor-Locke C, Zhang Y, Niu J, Felson DT, Gross KD, et al. Prospective change in daily walking over 2 years in older adults with or at risk of knee osteoarthritis: the MOST study. Osteoarthr Cartil [Internet]. 2016 Feb;24(2):246–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26318659

67. van Helvoort EM, Hodgins D, Mastbergen SC, Marijnissen AK, Guehring H, Loef M, et al. . Relationship between motion, using the GaitSmartTM system, and radiographic knee osteoarthritis: an explorative analysis in the IMI-APPROACH cohort. Rheumatology (Oxford) [Internet]. 2021;60(8):3588–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33367896 [PubMed: 33367896]

68. Kim Y, Levin G, Nikolov NP, Abugov R, Rothwell R. Concept Endpoints Informing Design Considerations for Confirmatory Clinical Trials in Osteoarthritis. Arthritis Care Res (Hoboken) [Internet]. 2020 Dec 20; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33345469

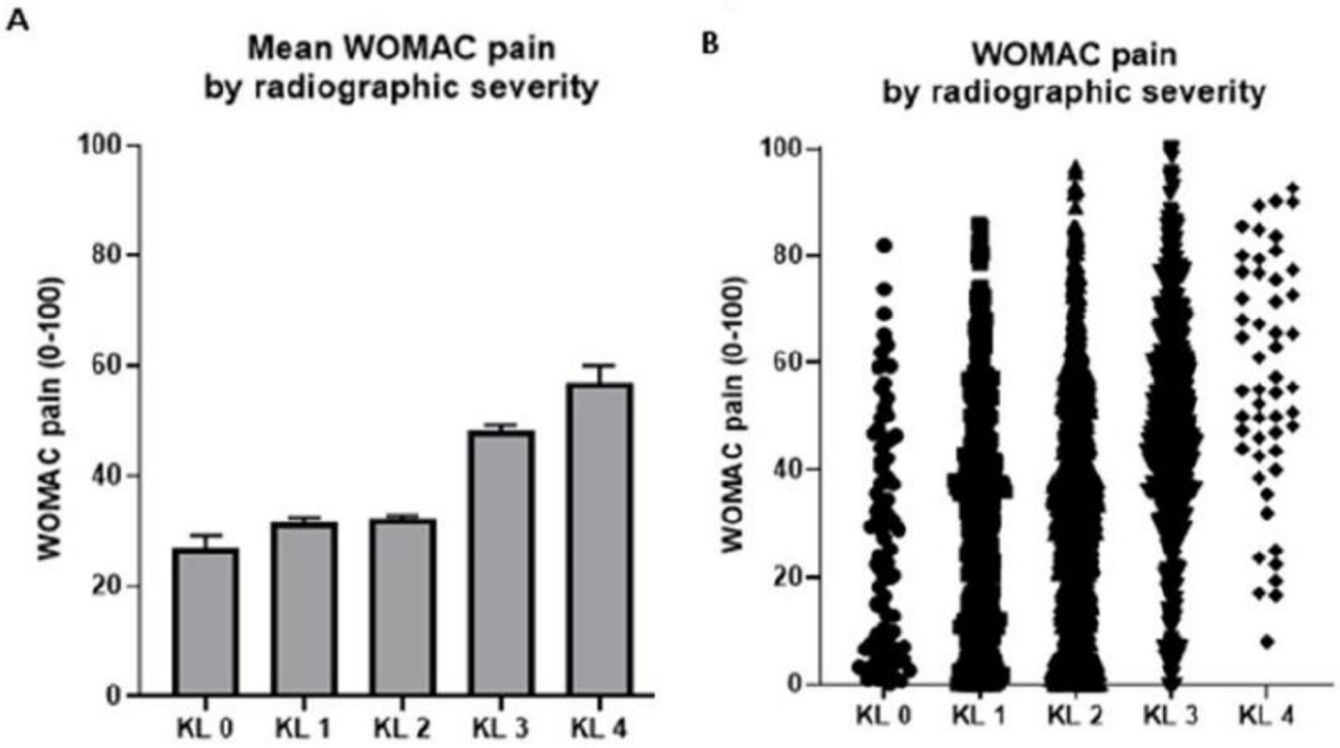

Figure 1:

Variability of pain in individuals with different degrees of structural severity. The two figures illustrate identical datasets of baseline WOMAC pain as a mean +standard error of the mean (SEM) (Figure A), and the same data as a point scatter plot (Figure B). Based on data on file from the OA oral Calcitonin studies, N=2,206, NBCD A/S and Nordic Bioscience A/S)(5)

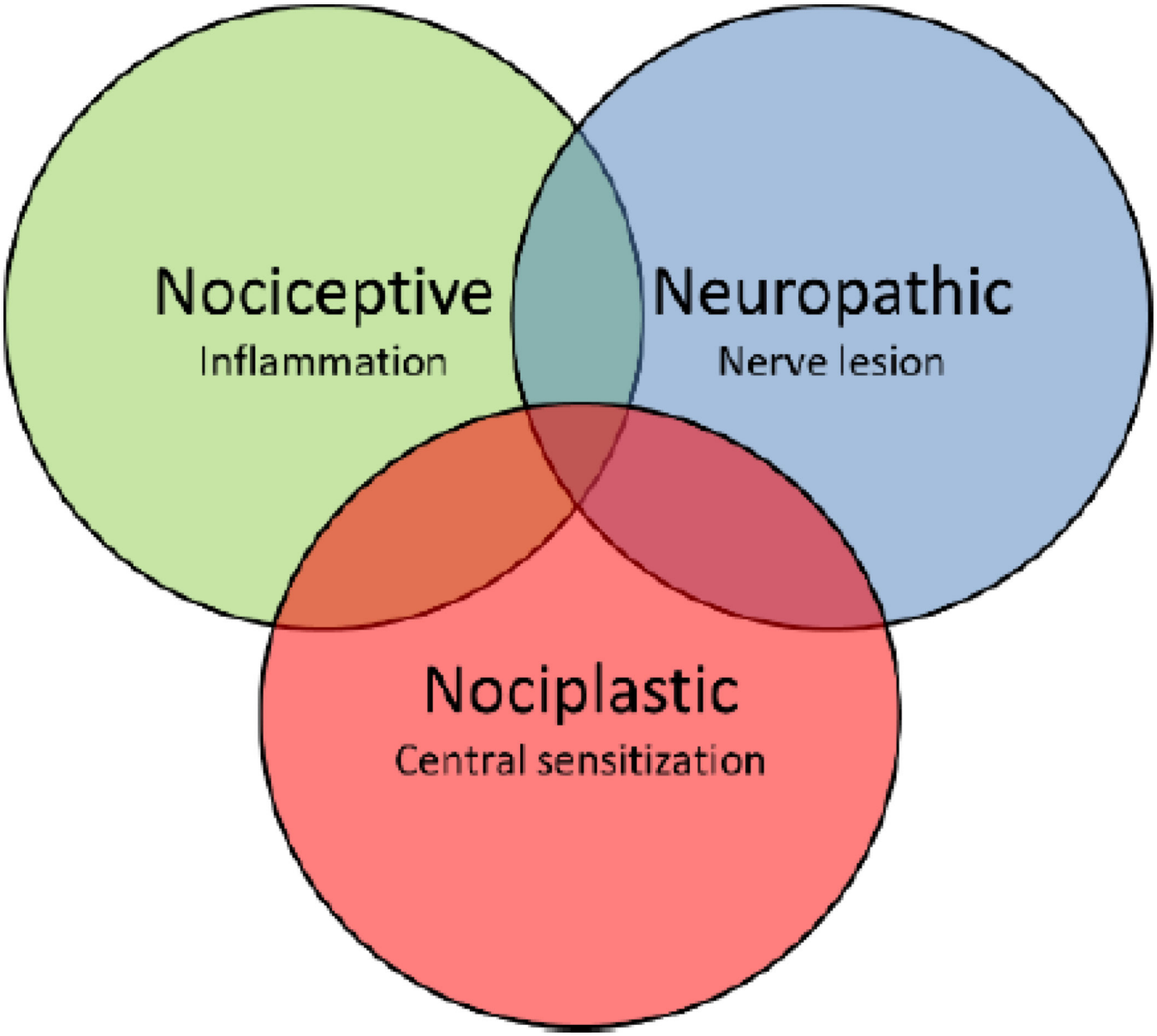

Figure 2:
Venn diagram of three types of pain and their overlap in OA. Nociceptive pain: Injury and inflammation. Neuropathic pain: Nerve lesion. Nociplastic pain: Central sensitization. These different pain types may show similar effect size on WOMAC but represent different pathologies that may need different treatments.

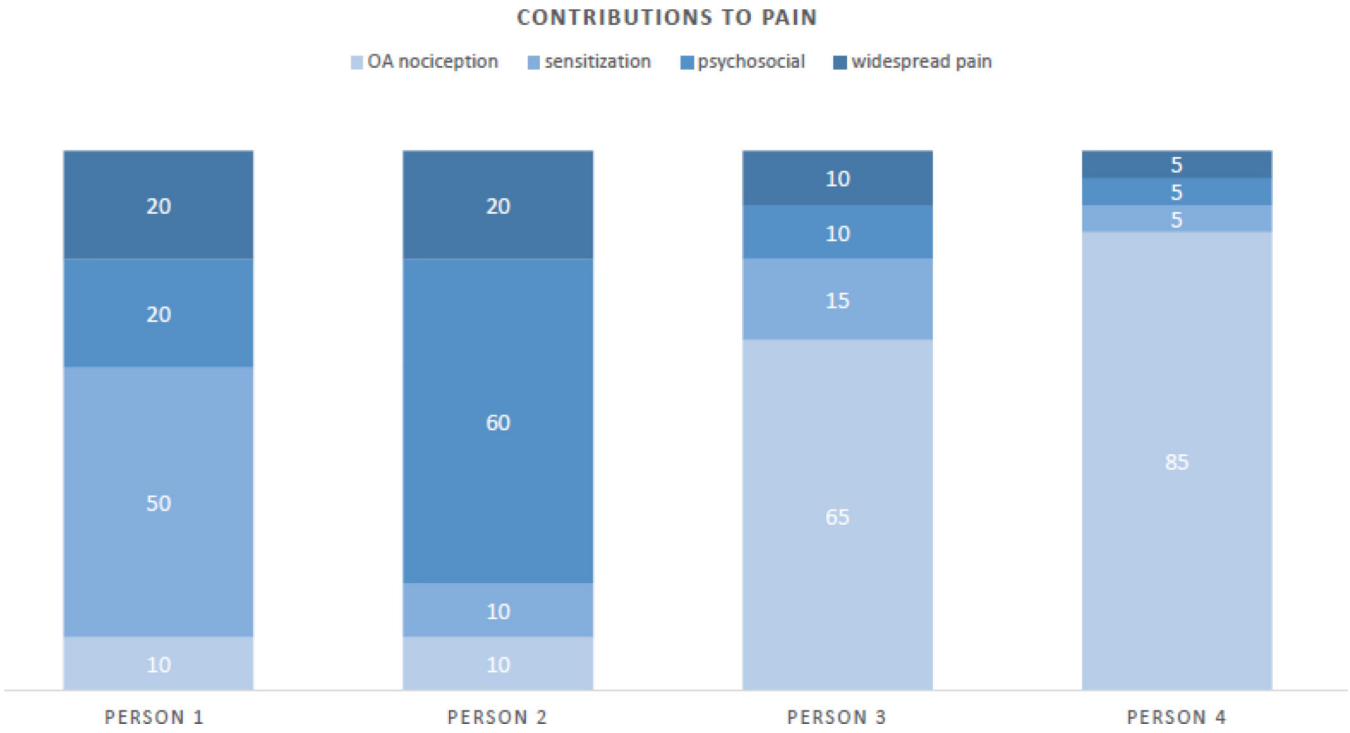

Figure 3:
hypothetical example of 4 potential study participants being considered for enrollment into a trial. The numerical values in the bars reflect the hypothetical relative proportion of mechanisms contributing to the individual's pain experience

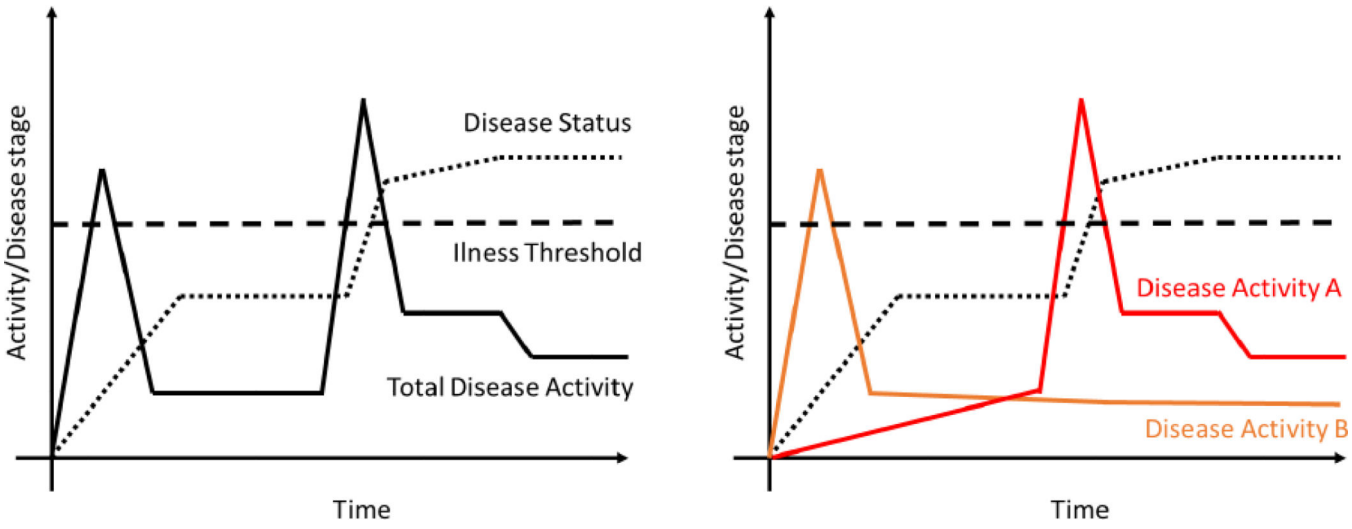

Figure 4:

Schematic illustration of disease activity versus disease status. A: Total disease activity may be independent of disease status. B: Targeting of intervention may need to consider periods of mechanism-based disease activity assessments that influence overall disease status rather than solely targeting based upon disease status without consideration of disease activity. Additionally, the treatment target should be matched to the specific mechanism contributing to the disease activity. Reproduced with permission from (1)

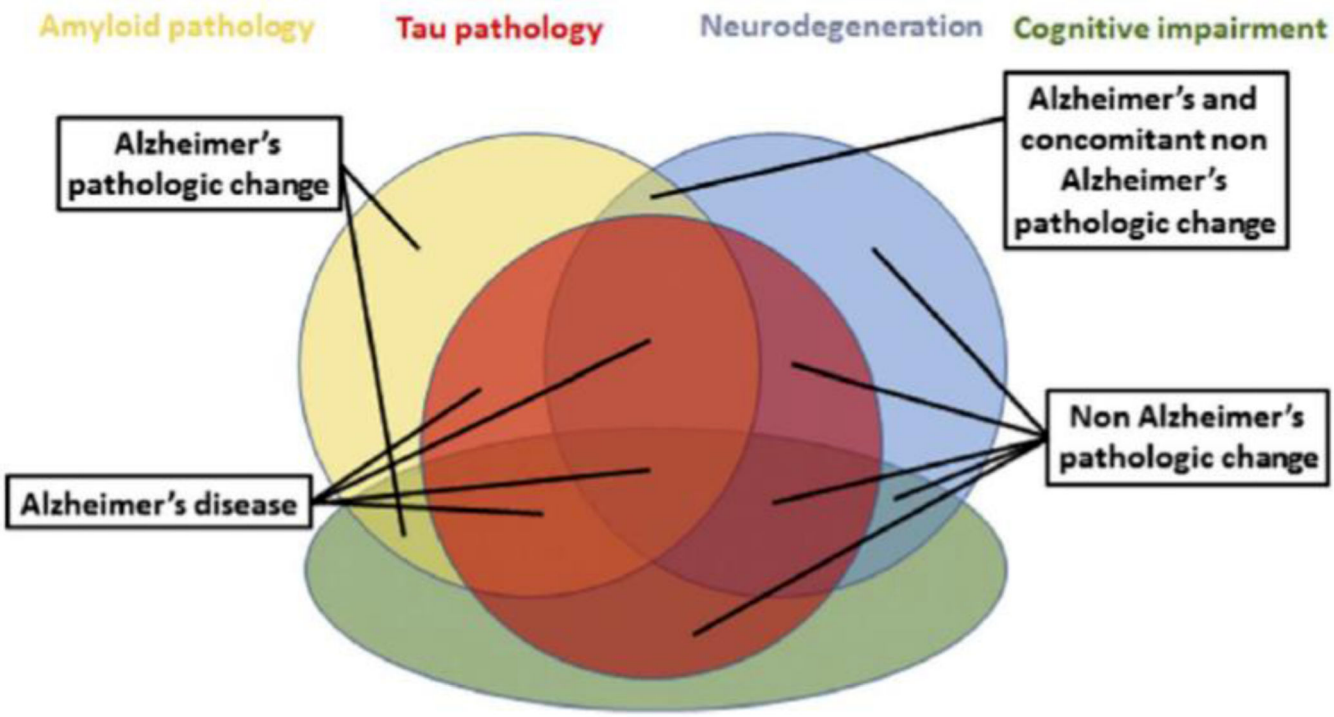

Figure 5:

Descriptive nomenclature Venn diagram. We illustrate how AT(N) biomarker grouping and cognitive status interact for classification of research participants in this Venn diagram. For simplicity, MCI and dementia are combined into a single (cognitively impaired) category and the A−T−(N)− groups are not shown. Also "Alzheimer's and concomitant non-Alzheimer's pathologic change" [A+T−(N)+] in cognitively impaired is not shown in this figure. Abbreviation: MCI, mild cognitive impairment. Reprinted with permission from (46).

Table 1.

Deconstructing Alzheimer's Disease: shifting from clinical to biomarker constructs of dementia syndromes - IA-AA 2018 classification criteria:

IA-AA 2018 criteria for dementias represent a paradigm shift in disease classification from clinical to biological (biomarker) constructs for dementia syndromes. This framework is designed for use in clinical trials and research only, and not for clinical practice. Reprinted with permission from (56).

		Cognitively Unimpaired	Mild Cognitive Impairment	Dementia
Biomarker profile	$A^{-}T^{-}(N)^{-}$	Normal AD biomarkers; cognitively unimpaired	Normal AD biomarkers with MCI	Normal AD biomarkers with dementia
	$A^{+}T^{-}(N)^{-}$	Preclinical Alzheimer's pathological change	Alzheimer's pathological change with MCI	Alzheimer's pathological change with dementia
	$A^{+}T^{+}(N)^{-}$	Preclinical Alzheimer's Disease	Alzheimer's Disease with MCI (Prodromal AD)	Alzheimer's Disease with dementia
	$A^{+}T^{+}(N)^{+}$			
	$A^{+}T^{-}(N)^{+}$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, with dementia
	$A^{-}T^{+}(N)^{-}$	Non-Alzheimer's pathologic change, cognitively unimpaired	Non-Alzheimer's pathologic change, with MCI	Non-Alzheimer's pathologic change, with dementia
	$A^{-}T^{-}(N)^{+}$			
	$A^{-}T^{+}(N)^{+}$			

Abbreviations: Aβ = amyloid; CSF = cerebrospinal fluid); A = aggregated Aβ or associated pathological state (CSF $A\beta_{42}$ or $A\beta_{42/40}$ ratio Amyloid PET); T = aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau, Tau PET); (N) = neurodegeneration, (anatomical MRI, FDG-PET, CSF total tau); AD = Alzheimer's Disease; MCI = mild cognitive impairment; Shaded area = AD continuum