**Can/should we use or develop large animal models (e.g., pigs, dogs) or naturally occurring companion models (i.e. cats, dogs, guinea pigs) to better replicate human obesity-associated OA phenotypes and mechanics?** Dianne Little

**Response:** Yes. No single animal or new approach methodology captures the full spectrum of human OA. However, compared to *in vitro, in silico*, and *in vivo* small animal mechanistic models, large animal models provide key advantages and opportunities for integration of the effects of biomechanical and metabolic factors related to obesity-associated OA over a potential lifespan of many years. Companion animal species (cats, dogs, guinea pigs, horses) have many of the same environmental exposures as their human owners, commonly have diet-induced obesity, and commonly have spontaneous OA. Similarly, other large animals species are frequently obese as a result of management under conditions of domestication, or are used as models of obesity. All large animal models either have high prevalence of naturally occurring osteoarthritis, or can be readily used for induced models of osteoarthritis, and in some species, links between obesity and osteoarthritis have been suggested.

**Level of Evidence:** Low

**Delegate Vote:** Agree: Disagree: Abstain:

**Rationale:**

*Large Animal Models of Induced and Spontaneous OA may be valuable in replication of human obesity-associated OA:* Large animal models have the potential to circumvent some of the disadvantages of small animal models of obesity-associated OA with regard to larger joint size, tissue structure, tissue turnover, and mechanical properties that more closely match those of human, joint biomechanics that are more similar to human, and closer anatomic and physiological similarity to human.[1-3] These factors make some assessments and outcome measures more viable, or more translationally relevant than in small animal models, and surgical techniques and interventions more closely representative of techniques used in human orthopaedic surgery.[1-3]

*Induced and Management-related Obesity are common in Large Animal Species:* The prevalence of non-communicable diseases, including obesity is rising in both domesticated and wild animals due to interactions of genetic factors, environmental exposures, and human-driven environmental change.[4] A number of swine models are widely used to evaluate metabolic complications and pathology in obesity, including spontaneous obesity related pathology in the Yucucan minipig, and Ossabaw pig.[5] Approximately 60% of pet cats and dogs are now classified as overweight or obese, with prevalence increasing.[4,6] Up to 72% horses are overweight or obese, with metabolic conditions, chronic inflammation, insulin dysregulation, and adipose tissue dysregulation commonly comorbid.[7] Horses also offer the unique advantage of being readily trained to carry substantial added loads, providing the ability to distinguish between the mechanical effects of additional bodyweight and the pathophysiology of the biological effects of increased adiposity.[7] In guinea pigs, approximately 23% of client-owned guinea pigs are obese, and a link between obesity and osteoarthritis has been proposed.[8]

*Spontaneous Osteoarthritis is highly Prevalent in Large Animal Companion Animal Species:* All large animal species frequently demonstrate spontaneous or age-related development of osteoarthritis that is slowly progressive over many years, and post-traumatic osteoarthritis is relatively common, with some species demonstrating similar injury mechanism to human (post-traumatic osteoarthritis, developmental orthopaedic disease, idiopathic age-related). [1,2] The prevalence of osteoarthritis in at least one joint of horses over the age of 15 or 30 is estimated to be around 51% and 77% respectively,[9] with pain (lameness) and reduced range of motion the most common findings on initial clinical examination.[10] Osteochrondral, cartilage, and articular soft tissue injuries are highly prevalent in horses during training or athletic competition, and in some cases, when feasible, are treated in similar ways as human athletes.[11,12] An estimated 20% of adult dogs have osteoarthritis, and while a link between obesity and osteoarthritis has been suggested, the effect of obesity on joint biomechanics in osteoarthritis remains unknown.[13] Moreover, the majority of examining obesity and osteoarthritis in the dog has evaluated the interactions between diet during growth from the perspective of modification of developmental orthopaedic diseases such as hip dysplasia.[13] In cats, a prevalence of 16-91% has been reported for radiographic OA in cats age 0.2-20 years, with over 25% cats overall

showing radiographic OA in at least one joint, but diagnosis of OA from clinical signs alone is more complex in cats than in most other large animal species.[14] The role of the infrapatellar fat pad in osteoarthritis has been evaluated in spontaneous osteoarthritis in the Dunkin-Hartley guinea pig.[15]

*A wide variety of Induced OA models are reported in large animal species:* Depending on specific species, anterior (cranial) cruciate ligament transection, meniscal injury, medial collateral ligament injury, medial femoral condyle defect models, osteochondral fragment models, femoral head defect models, and intra-articular fracture. [16-18] In many cases, outcome measures can be evaluated for both induced and spontaneous OA that are very sensitive at identifying changes in pain, gait, function, and activity.[18-20]

*Ethical Considerations in Induced and Spontaneous Large Animal Models:* Use of animal models in general, and particularly animal models in species widely considered to be companion animal species has become increasingly controversial in recent years,[2] with increasing public debate and funding agency scrutiny. However, given the complexities of the genome, of genome x environment x intrinsic variable (e.g. aging) interactions, and of systemic physiology, animal models are still a critical component, and for regulatory purposes, a mandatory component of translational research, which cannot yet be replaced by new approach methodologies.[2] Therefore, as is true when any animal model is used, all of the principles of replacement, reduction, and refinement should be fully implemented, studies should be carefully designed and performed to maximize animal welfare, the amount of usable data obtained from each animal, and to improve reproducibility and standardization,[21] and data should be fully reported in accordance with recognized guidelines such as ARRIVE.[22] Experimental interventions in companion animals with naturally occurring disease that are client-owned should have careful independent oversight, must ensure that the owner is fully informed and consented regarding the proposed procedures or intervention, regarding any deviation from clinical standard of care (if applicable), and must ensure that adequate safety monitoring is in place so that adverse events can be detected and managed early to ensure the best possible outcome. The principles of *primum non nocere*, 'Do no harm' and veterinary medical ethics in the relevant jurisdiction apply, in addition to relevant laboratory animal regulations for example, the American Veterinary Medical Association[23], or the Royal College of Veterinary Surgeons[23] in the United Kingdom. High resolution outcome measures and in silico modeling should be used wherever possible to facilitate implementation of these principles.

*Limitations of Induced and Spontaneous Large Animal Models:* No animal model can precisely recapitulate human OA phenotypes, and in some cases, the disease mechanism of spontaneous OA may be different in large animals and human. For example, anterior (cranial) cruciate ligament tear is most commonly a traumatic injury event in humans and horses, but in dogs, cranial cruciate ligament tear is a degenerative event, leading to different OA trajectories. As for human OA, the disease trajectory in spontaneous large animals may be many years for clinical OA to appear, making long term monitoring expensive and in some cases challenging. Nonetheless, with careful consideration of these limitations, and the appropriate level of veterinary expertise, induced and spontaneous large animal models have the potential be extremely useful in understanding of obesity-induced OA phenotypes.

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