A Novel Intra-articular Therapy for Canine Elbow Osteoarthritis – Part 2

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MedVet Columbus

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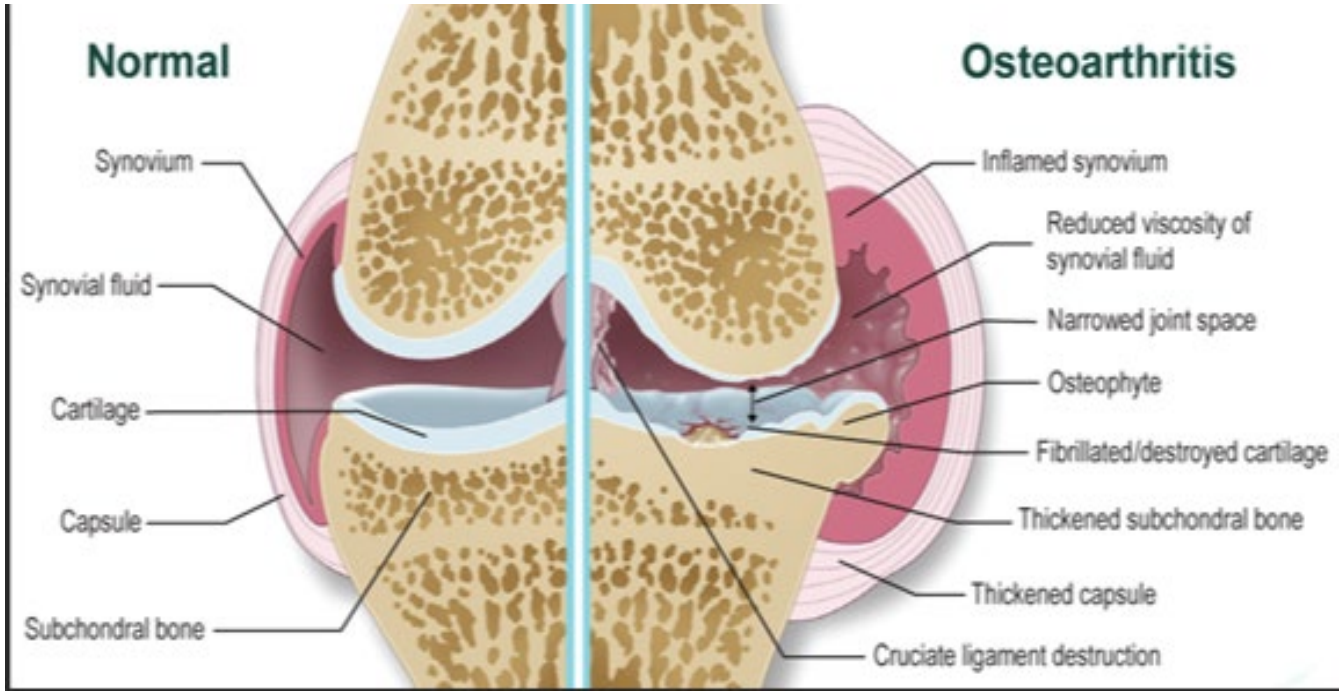
Leading Specialty Healthcare for Pets

Osteoarthritis (OA)

- 20,000,000 of all canines in the US are affected
- 2,000,000 → referred to see specialists
- 900,000 → actually see a specialists
- 600,000 → actually get proper treatment



Canine OA Pain Management: 2 Major Gaps

Daily Drugs
- Ineffective for many
- Long-term safety issues
- Poor compliance

Therapeutic Gap
No durable, proven intermediate treatment options

Joint Replacement
- Not for all joints
- High risk for older pets
- Disruptive rehab

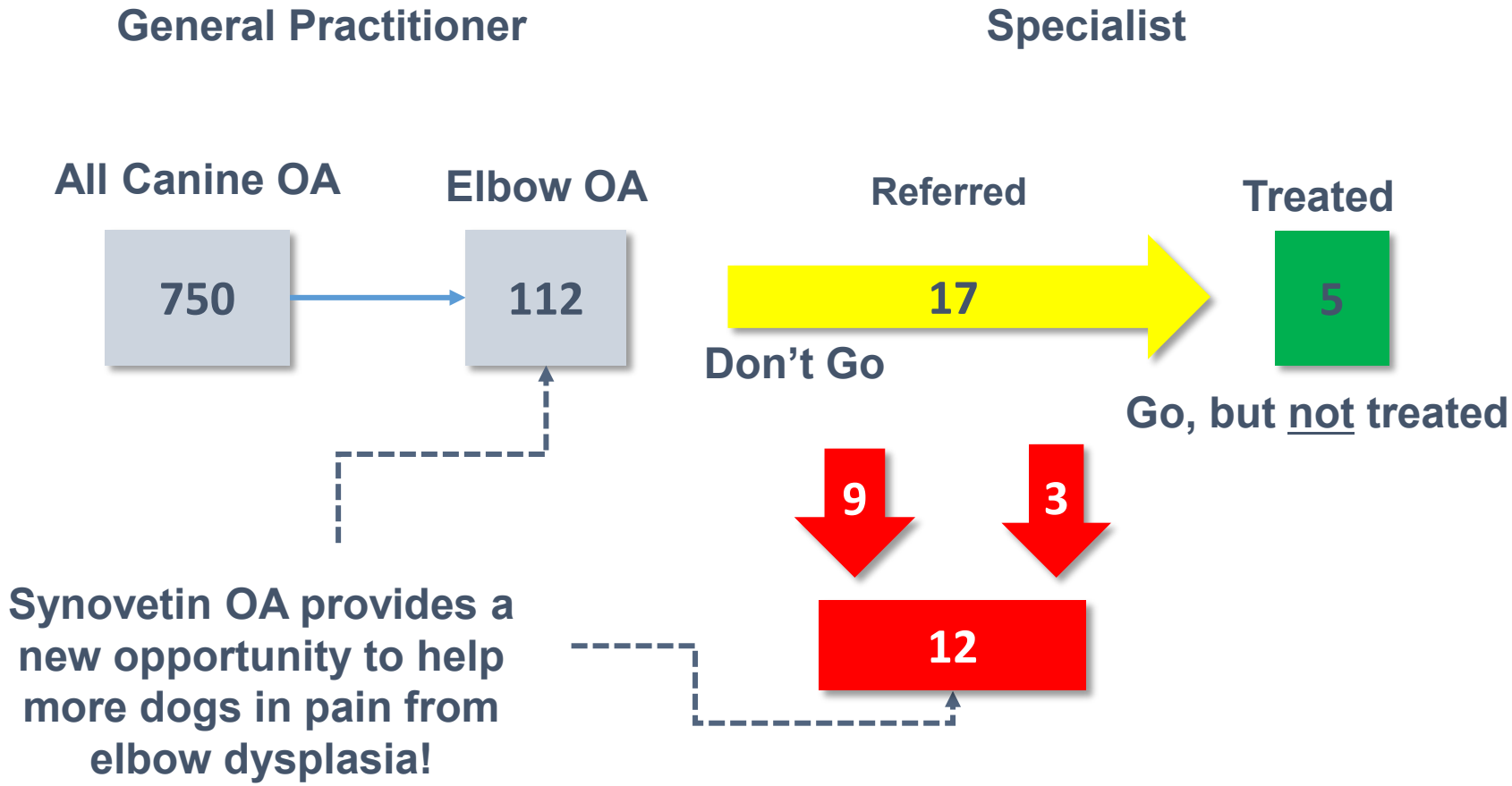
General Practices

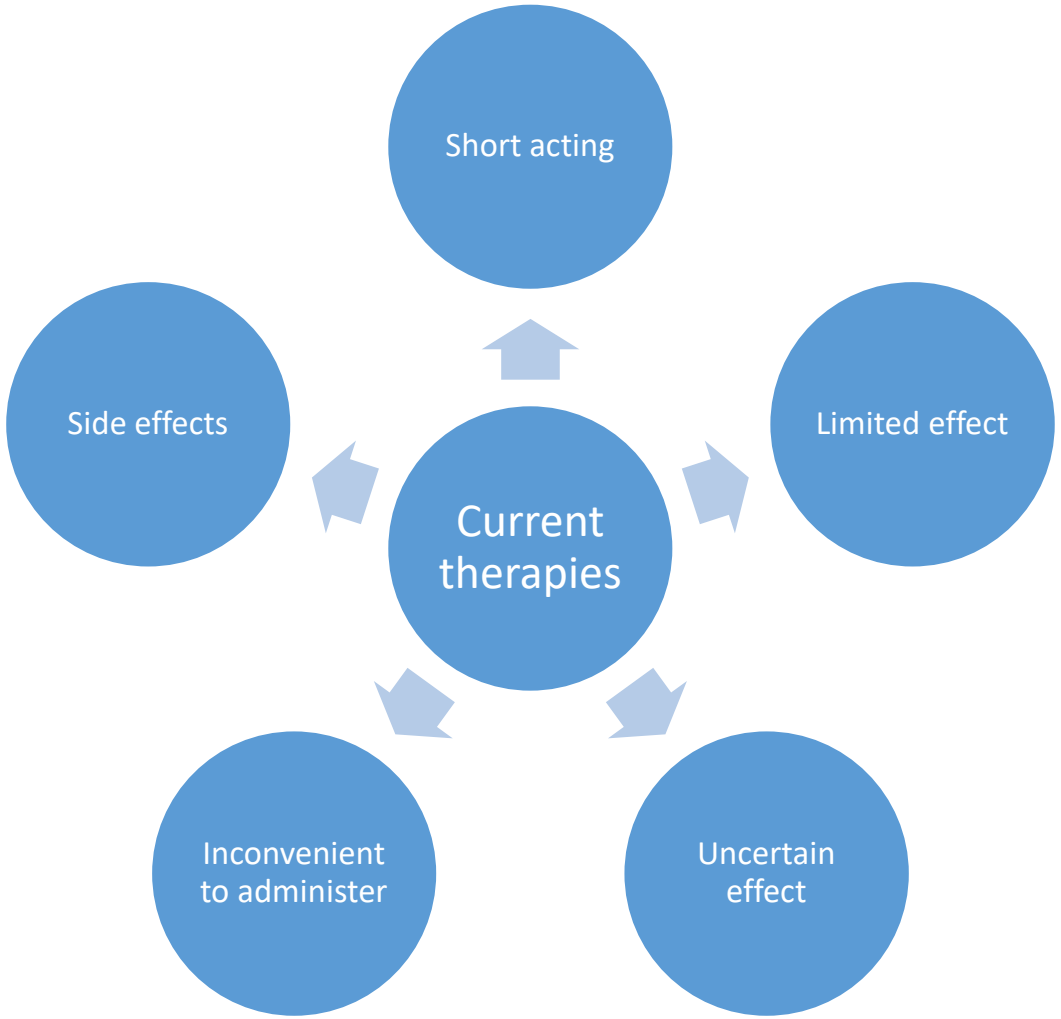
$4.2B Veterinary Revenue Gap
~2M cases / year referred
only ~0.6M treated[1]

Specialty Hospitals

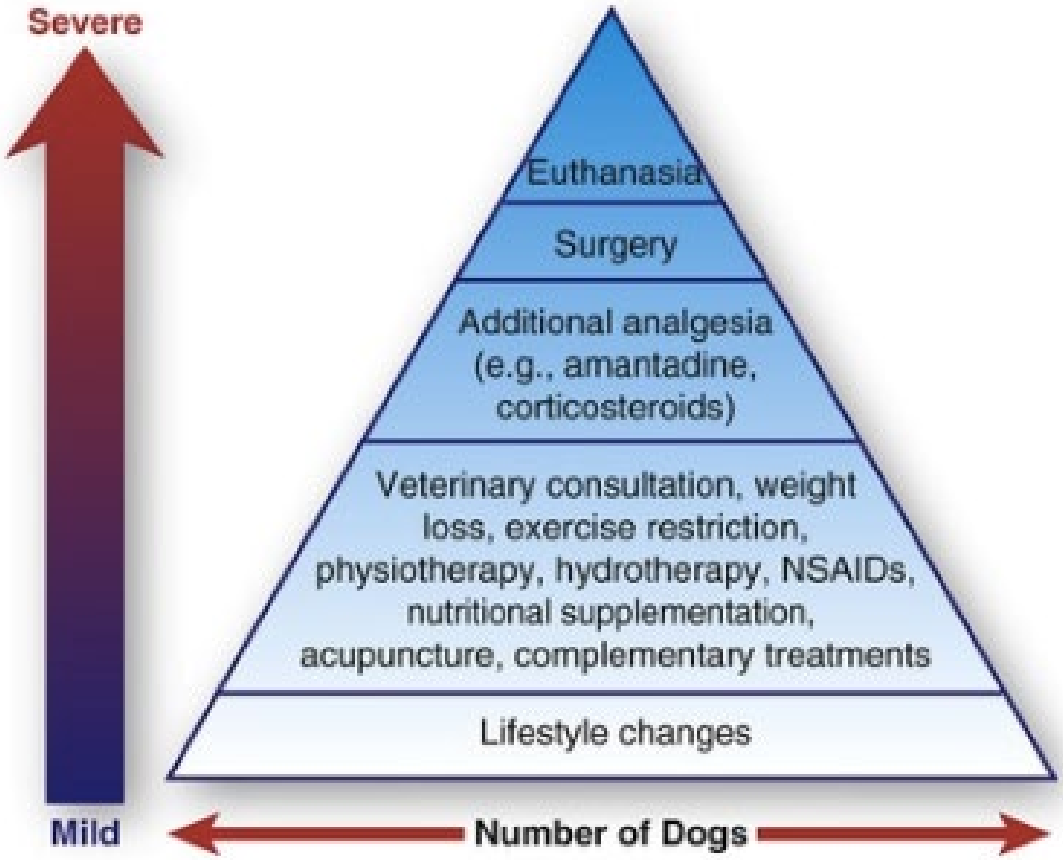
[1]Harmony Marketing Partners survey results, 2016

Management of OA




Short acting
Side effects
Limited effect
Current therapies
Inconvenient to administer
Uncertain effect

TYPE	Examples	Pros	Cons
NSAID	Carprofen, Deramaxx	Decreases pain and inflammation, PRN	Owner compliance, multiple doses needed, GI upset, ulcers, kidney disease
Analgesics	Amantadine, Gabapentin, hydrocodone	PRN, minimal side effects	Owner compliance, multiple doses needed, controlled drugs/owner misuse
Corticosteroids	Intra-articular dexamethasone	Pain control, easy to perform	Duration varies
Polysulfated glycosaminoglycan	Adequan	Monthly, owners can do at home	Aids to help with discomfort but doesn't full rid pain
Nutraceuticals Functional food	Chondroitin, Glucosamine Essential fatty acids, veterinary prescription diets	Daily medication or added to food	Owner compliance, lacks data
Mesenchymal stem cells	Multipotent stem cells	Differentiate into any cell type-chrondrocytes, osteoblasts, etc	Need to be harvested via surgery, expensive



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Osteoarthrosis/Osteoarthritis

Most common clinical disorder

- Progression
  - Synovial inflammation – earliest stage of joint degeneration
  - Ligamentous and capsular injury
  - Cartilage injury
  - Subchondral and perichondral bone injury – latest stage of disease

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OA and Synovial Macrophages

The role of synovial macrophages and macrophage-produced cytokines in driving aggrecanases, matrix metalloproteinases, and other destructive and inflammatory responses in osteoarthritis

Bondeson J, Wainwright SD, Lauder S, et. al. Arthritis Research & Therapy 7 2006 8:R187(doi:10.1.186/ar2099)

- Synovial inflammation is implicated in many signs and symptoms of OA, including joint swelling and effusion
- In the osteoarthritis synovium, both inflammatory and destructive responses are dependent largely on macrophages and these effects are cytokine driven through a combination of IL-1 and TNFα
- These cytokines can stimulate their own production and induce synovial cells and chondrocytes to produce IL-6, IL-8, leukocyte inhibitory factor; as well as stimulate protease (matrix metalloproteinases (MMPs) and aggrecanases) and prostaglandin production

❖ **"Results suggest prioritization of attempts to modify macrophage function in OA, with the aim of decreasing both inflammatory synovitis and the production of degradative enzymes (cytokines) of importance for the progression of the disease"**

Synovitis is prevalent in OA and precedes radiographic OA

Synovitis drives structural changes in OA

Macrophages and synoviocytes are overproduced in synovitis

Inflammatory mediators are secreted which destroy cartilage and drive more synovitis (Vicious Cycle)

New treatments that target macrophages reduce synovitis and pain

Therapeutic Advances in Musculoskeletal Disease Review

The role of synovitis in osteoarthritis

Ther Adv Musculoskel Dis
(2010) 2(6) 349–359
DOI: 10.1177/1759720X10378373

Claire Y. J. Wenham and Philip G. Conaghan

Abstract: Osteoarthritis (OA) is the most common form of arthritis worldwide yet there is still a lack of effective treatments for this condition. Increasingly, attention has turned to the role of the synovium in OA as it is now recognized, in part from the use of modern imaging techniques, that synovitis is both common and associated with pain. This offers a target for treatment, for both symptom and potential structure modification. In this review we discuss the

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Macrophages regulate the progression of osteoarthritis

H. Zhang †, D. Cai † **, X. Bai † ‡ § *

† *Department of Orthopedics, Orthopedic Hospital of Guangdong Province, Academy of Orthopedics-Guangdong Province, Guangdong Provincial Key*

ARTHRITIS & RHEUMATISM
0, pp 647–657
of Rheumatology

M J Benito, D J Veale, O FitzGerald, W B van den Berg, B Bresnihan

Ann Rheum Dis 2005;**64**:1263–1267. doi: 10.1136/ard.2004.025270

Synovitis in Dogs with Stable Stifle Joints and Incipient Cranial Cruciate Ligament Rupture: A Cross-Sectional Study

Jason A. Bleedorn[1,2], DVM, Diplomate ACVS, Erin N. Greuel[1], BS, Paul A. Manley[1,2], DVM, MSc, Diplomate ACVS, Susan L. Schaefer[1,2], DVM, MS, Diplomate ACVS, Mark D. Markel[1,3], DVM, PhD, Diplomate ACVS, Gerianne Holzman[4], CVT, and Peter Muir[1,2], BVSc, MVetClinStud, PhD, Diplomate ACVS & ECVS

[1]Comparative Orthopaedic Research Laboratory, School of Veterinary Medicine, University of Wisconsin–Madison, Madison, WI, [2]Department of Surgical Sciences, School of Veterinary Medicine, University of Wisconsin–Madison, Madison, WI, [3]Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin–Madison, Madison, WI and [4]Veterinary Medical Teaching Hospital, School of Veterinary Medicine, University of Wisconsin–Madison, Madison, WI

Research article **Open Access**

The role of synovial macrophages and macrophage-produced cytokines in driving aggrecanases, matrix metalloproteinases, and other destructive and inflammatory responses in osteoarthritis

Jan Bondeson[1], Shane D Wainwright[2], Sarah Lauder[1], Nick Amos[1] and Clare E Hughes[2]

[1]Department of Rheumatology, Cardiff University, Heath Park, Cardiff, CF14 4XN, UK
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Radionuclide Tin-117m (Synovetin OA)

Synovetin OA® is marketed by:

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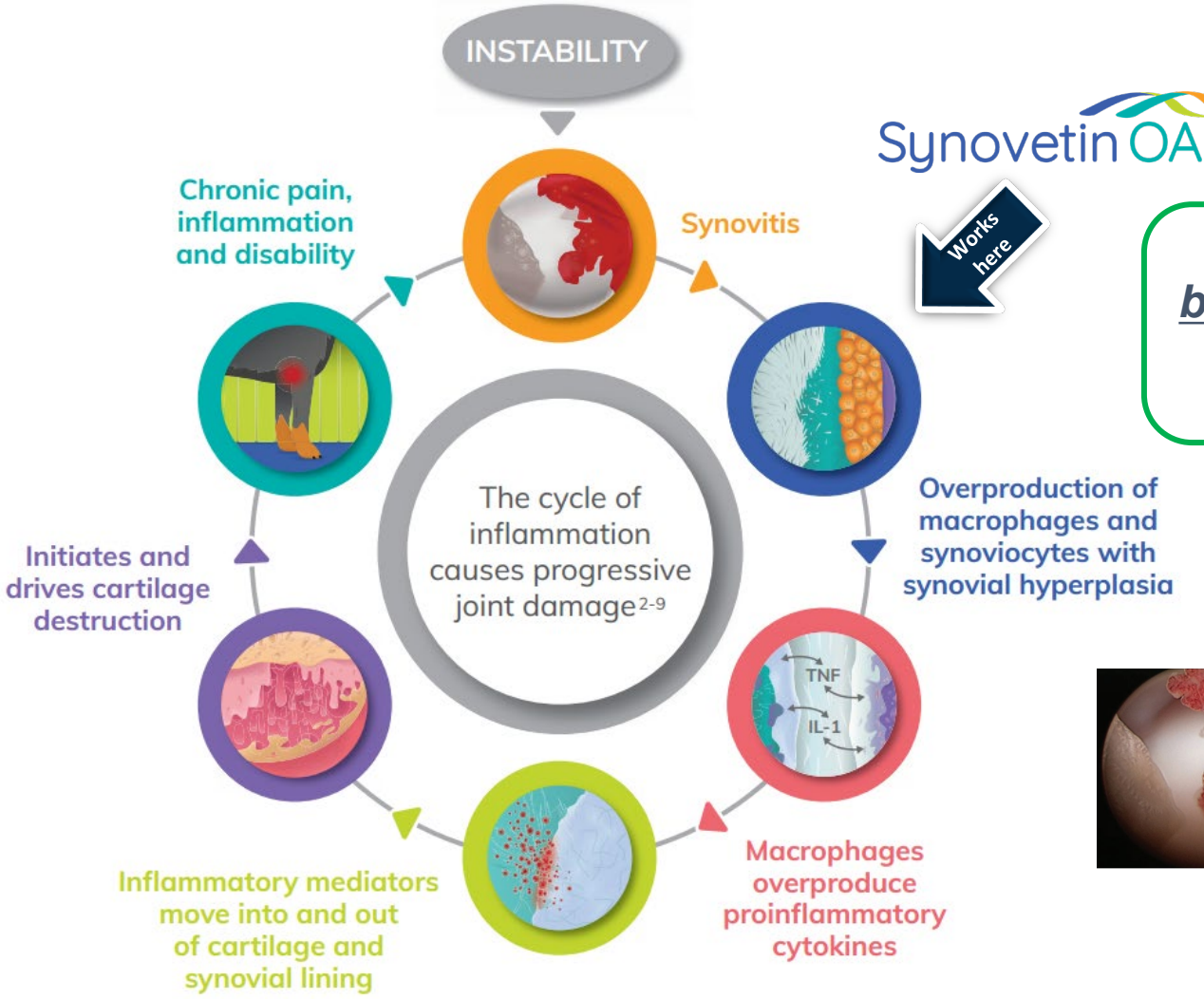
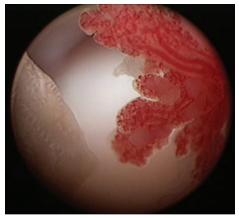
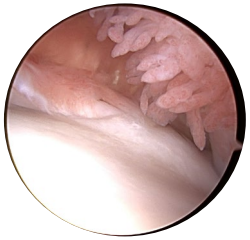


Synovetin OA

Works here

Synovetin OA®
breaks the vicious cycle
of inflammation
and chronic pain





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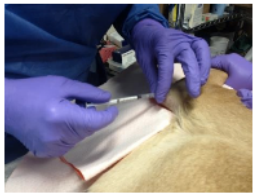
Radionuclide Tin-117m

- Reduces synovitis and relieves canine elbow AO pain
- Novel radio-isotope: Tin-117m
- Conversion electron radiation
- 0.3 mm penetration
- Half-life of 14 days
- Leaves via lymphatics



Comparison	Tin-117m	Iodine-131
Indication	OA	Feline hyperthyroidism
Administration	Local device	Systemic drug
Radionuclide distribution	Intra-articular	Systemic (sc/po)
Isolation	Not required	Required

Synovetin OA Radio·synovi·orthèses

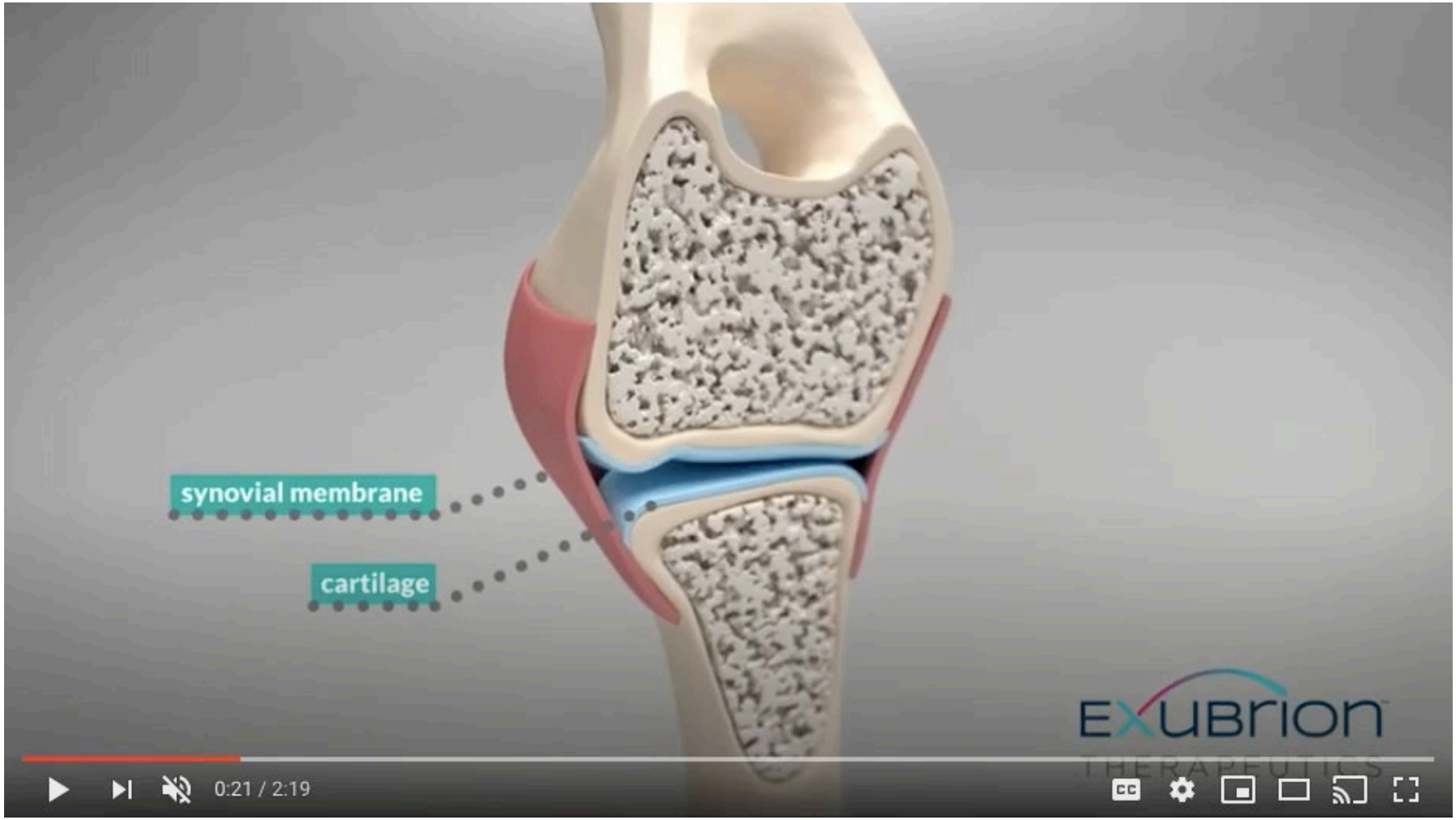
What is radiosynoviorthesis (RSO)? Intra-articular injection of radioisotope (radionuclide) to treat joint inflammation

Mode of action: Radionuclide is absorbed by synoviocytes and phagocytized by macrophages within the synovium resulting in apoptosis and non-inflammatory ablation of inflammatory cells

The homogeneous tin colloid suspension (1.5 – 20 µm) of tin-117m emits discrete (0.3 mm radiation range), low-energy conversion electron radiation

The colloid containing micro particles is retained in the canine joint space for at least 42 days (3 half-lives)

Mechanism of cell death from Synovetin OA is from extended duration ($T_{1/2}$ = 14d) low energy radiation (<158 keV) exposure effects


synovial membrane
cartilage
0:21 / 2:19
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Synovetin OA

Breaks the vicious cycle of inflammation that drives OA pain and progression

- ✓ Can provide **ONE YEAR** of effectiveness with only **ONE DOSE**
- ✓ 92% treatment success in mild-moderate OA
- ✓ Non-systemic, targeted therapy
- ✓ No clinically significant systemic or local side effects
- ✓ Multimodal
- ✓ Outpatient (IA-injection)
- ✓ Radiotherapeutic veterinary device (tin-117m)

Effective
Long lasting
Safe
Convenient

www.synovetin.com

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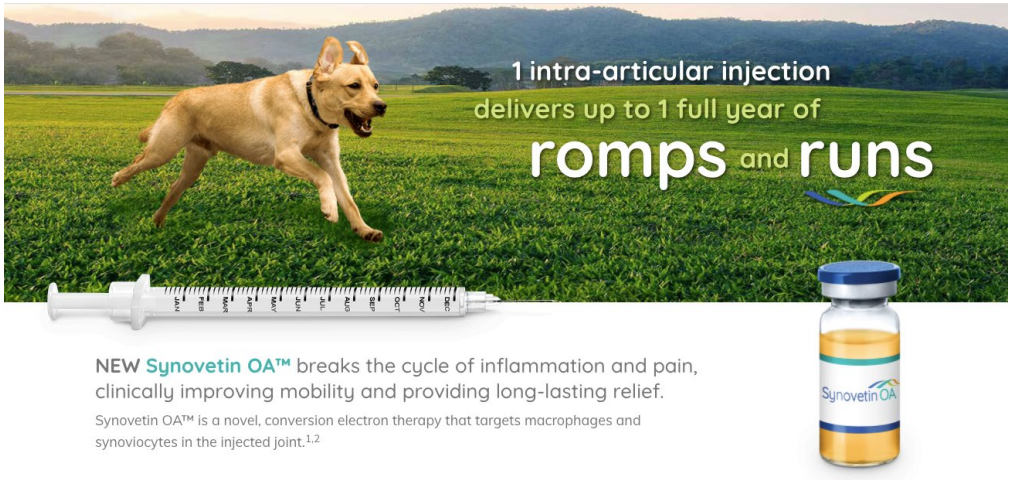

NEW Synovetin OA™ breaks the cycle of inflammation and pain, clinically improving mobility and providing long-lasting relief.

Synovetin OA™ is a novel, conversion electron therapy that targets macrophages and synoviocytes in the injected joint.[1,2]

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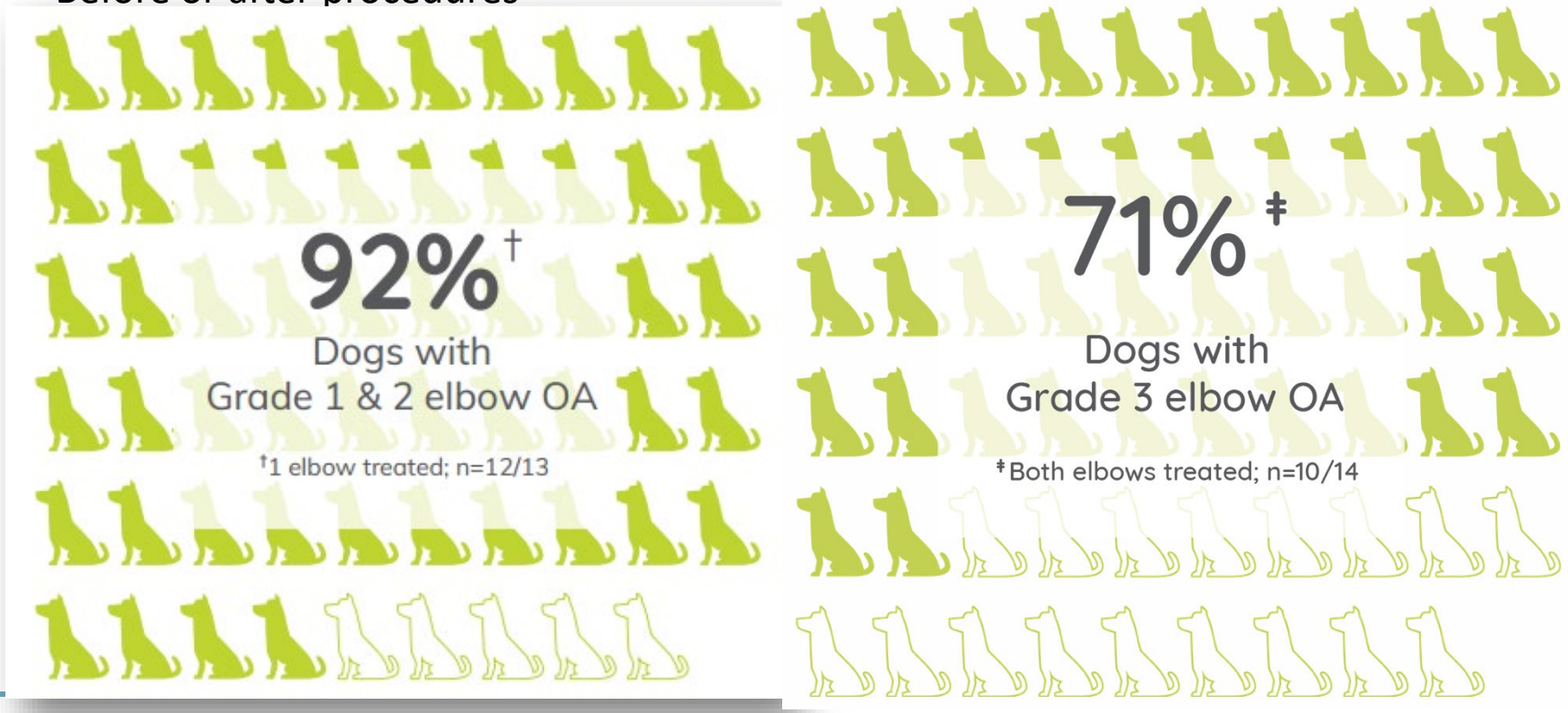
Ideal Times to Use Radionuclide Tin-117m

- Conservative therapy from beginning
- Failure of conservative therapy
- Before or after procedures



How Effective is Synovetin OA™?

- ✓ **Canine Brief Pain Inventory**
  - Client survey about reduction in pain and level of activity
  - Each time point survey compared to baseline survey results
  - 37 dogs initially treated with the label dose of Synovetin OA
- ✓ **9 months results**
  - 20/32 (62%) both pain AND level of activity improved successfully
  - 25/32 (78%) one OR other improved successfully with NO worsening of the other
- ✓ **12 months results**
  - 16/31 (52%) both pain AND level of activity improved successfully
  - 24/31 (77%) one OR other improved successfully with NO worsening of the other

How Effective is Synovetin OA™ ?

- ✓ **Force plate analysis of Grade 1 or 2 elbow OA (single leg injection)**
  - 22 dogs with grade 1 or 2 elbow OA in which the most painful elbow was injected
  - ≥ 5% positive change in PVF or VI considered a successful treatment effect
  - Each dog served as its own control comparing each time point to initial baseline data
  - 3 different dosages (1.0, **1.75** and 2.5 mCi per joint for 50 lb. dog)
  - 18/22 (82%) treatment effect at one or more time points
- ✓ **1 month –** 9/22 (41%) treatment success
- ✓ **3 months –** 13/22 (59%) treatment success
- ✓ **6 months –** 13/21 (62%) treatment success
- ✓ **9 months –** 11/18 (61%) treatment success
- ✓ **12 months –** 4/13 (31%) treatment success

How Effective is Synovetin OA™ ?

- ✓ **Force plate analysis of Grade 1 or 2 elbow OA (elbow reinjection)**
  - 10 dogs with grade 1 or 2 elbow OA in which both affected elbows were injected
  - ≥ 5% positive change in PVF or VI considered a successful treatment effect
  - Each dog served as its own control comparing each time point to initial baseline data
  - Label dosed (1.75 mCi per joint in a 50 lb. dog)
  - Baseline, 3 and 6 month force plate evaluations only
  - 6/9 (67%) treatment effect at one or more time points
- ✓ **3 months –** 5/9 (56%) treatment success
- ✓ **6 months –** 6/9 (67%) treatment success

How Effective is Synovetin OA™?

- ✓ **Clinician's lameness assessment (single leg injected)**
  - Lameness grading from 0 – 5 (worst)
  - Evaluated at walk and trot before and after joint manipulation
  - Each dog served as its own control comparing each time point to initial baseline data
  - 34 dogs in the Per Protocol group
  - 3 different dosages (1.0, **1.75** and 2.5 mCi per joint for 50 lb. dog)
- ✓ **9 months –** changes from baseline, indicating improvement from baseline, were found to be statistically significant (n=18)
- ✓ **12 months –** changes from baseline, indicating improvement from baseline, were found to be statistically significant (n=19)
- ✓ **McNemars test** –the comparison of cBPI success to clinician-assessed lameness success comparing baseline to each visit indicated statistical agreement.

Recommended Best Use - **EARLY INTERVENTION**

MILD TO MODERATE OA, EARLY ELBOW DYSPLASIA

"When NSAIDS aren't the answer"

- ✓ With or in place of NSAIDs
- ✓ At NSAID failure
- ✓ When NSAIDs can cause safety issues
- ✓ When compliance may be an issue
- ✓ To reduce NSAID use

Other uses:

In place of PRP or stem cells

Previously scoped dogs

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Radiation Synovectomy Using ^{188}Re-Tin Colloid Improves Knee Synovitis as Shown By MRI in Refractory Rheumatoid Arthritis

Shin, et al. Nuclear Medicine Communications: April 2007- Volume 28- Issue 4

- Overall improvement
  - Pain intensities lower
  - Improved joint effusion
  - Increased range of motion
  - Decreased pain
  - Decreased synovial thickening

Intra-articular Injection of a Tin-117m Radiosynoviorthesis Agent in Normal Canine Elbows Causes No Adverse Effects

Lattimer, et al. Vet Radio Ultrasound 2019; 60

- >99.1% of radionuclide Tin-117m activity was retained in the joint for ~45 days
- Absence of joint damage/systemic effects → safely used for radiosynoviorthesis in dogs with osteoarthritis
- 1, 3, 6, 9, 12 mos.
- All safety measures were within expected norms
- **No clinically significant treatment-related local or systemic adverse effects**

- 50K similar procedures done in people each year*

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The Use of tin-117m colloid for Treatment of Naturally Occurring Grade 3 Osteoarthritis of the Elbow in Client Owned Dogs

Fabiana, et al. July 2018

- 12 month study
- 15 dogs with Grade 3 OA had a treatment success rate of 71.4%
- Safety: no systemic or local side effects noted

Force Plate Analysis

Force plate gait analysis—Grade 1 & 2 Elbow OA

82% of dogs showed significant increase in peak vertical force and/or mean vertical impulse after just 1 injection.[2§]

Measurements taken at 1, 3, 6, 9, and 12 months.
Treatment Success = an improvement in PF and/or IMP during follow-up visit compared to baseline. n=22 dogs
PF=peak vertical force;
IMP=mean vertical impulse

Exubrion Therapeutics

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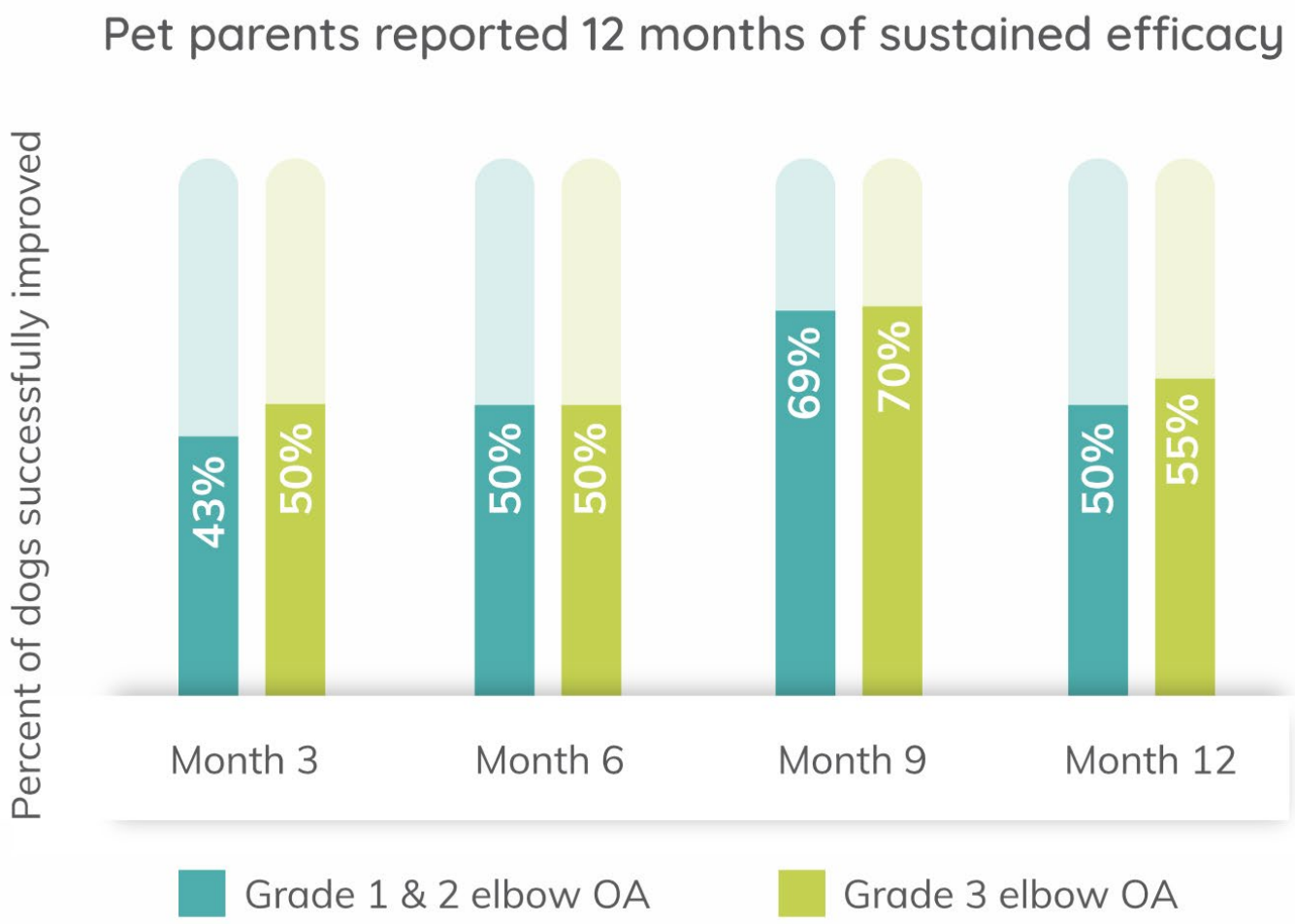
Owner and Clinician Pain scores



EXUBRION THERAPEUTICS

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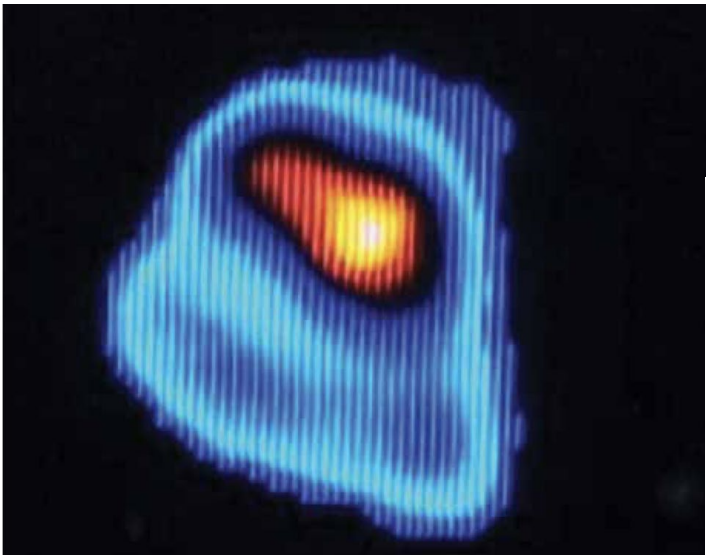
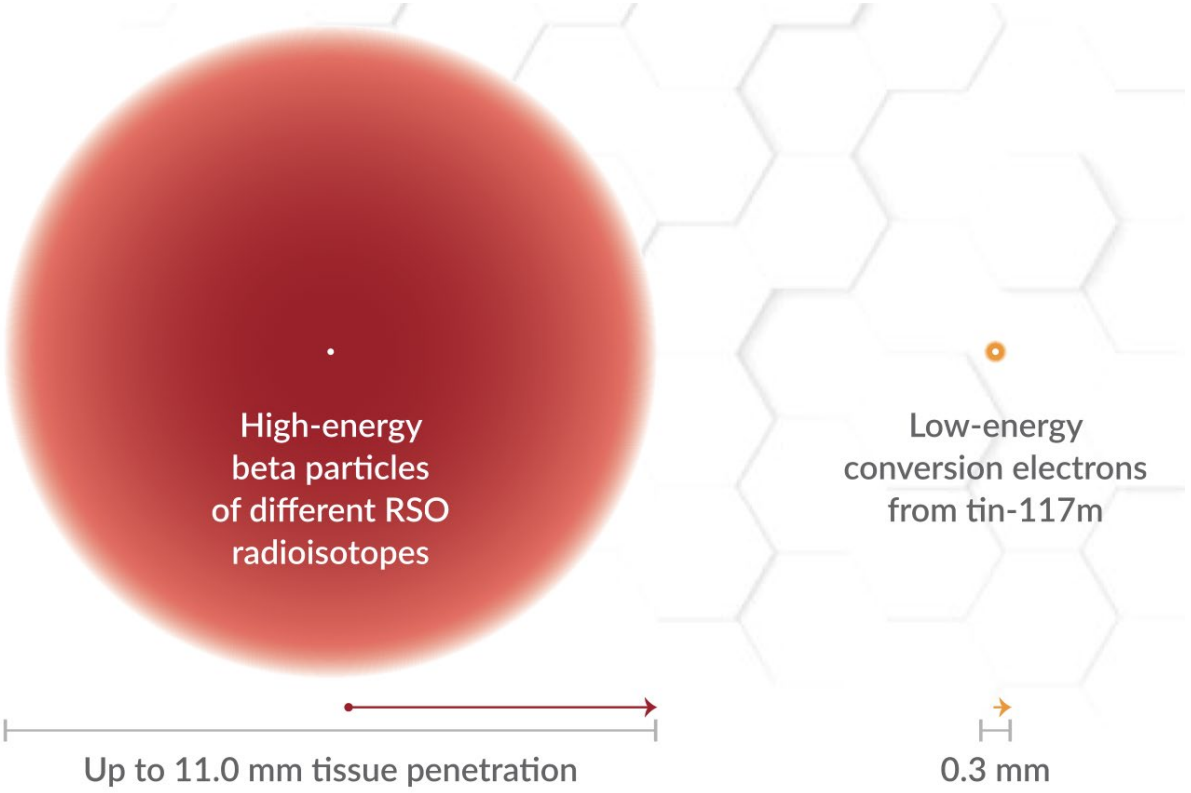
Re-injection of tin-117m Colloid in Naturally Occurring Grade 1 or 2 Osteoarthritis of the Elbow in Client Owned Dogs

Fabiana, et all. July 2018

- 12 month study
- 44 dogs with Grade 1 or 2 elbow OA had a treatment success rate of 88.2%
- 10 dogs retreated with Synovetin OA one year after an initial dose had a 66.7% treatment success rate
- Safety: no systemic or local side effects noted with therapy

Depth of penetration of tin 117M electrons





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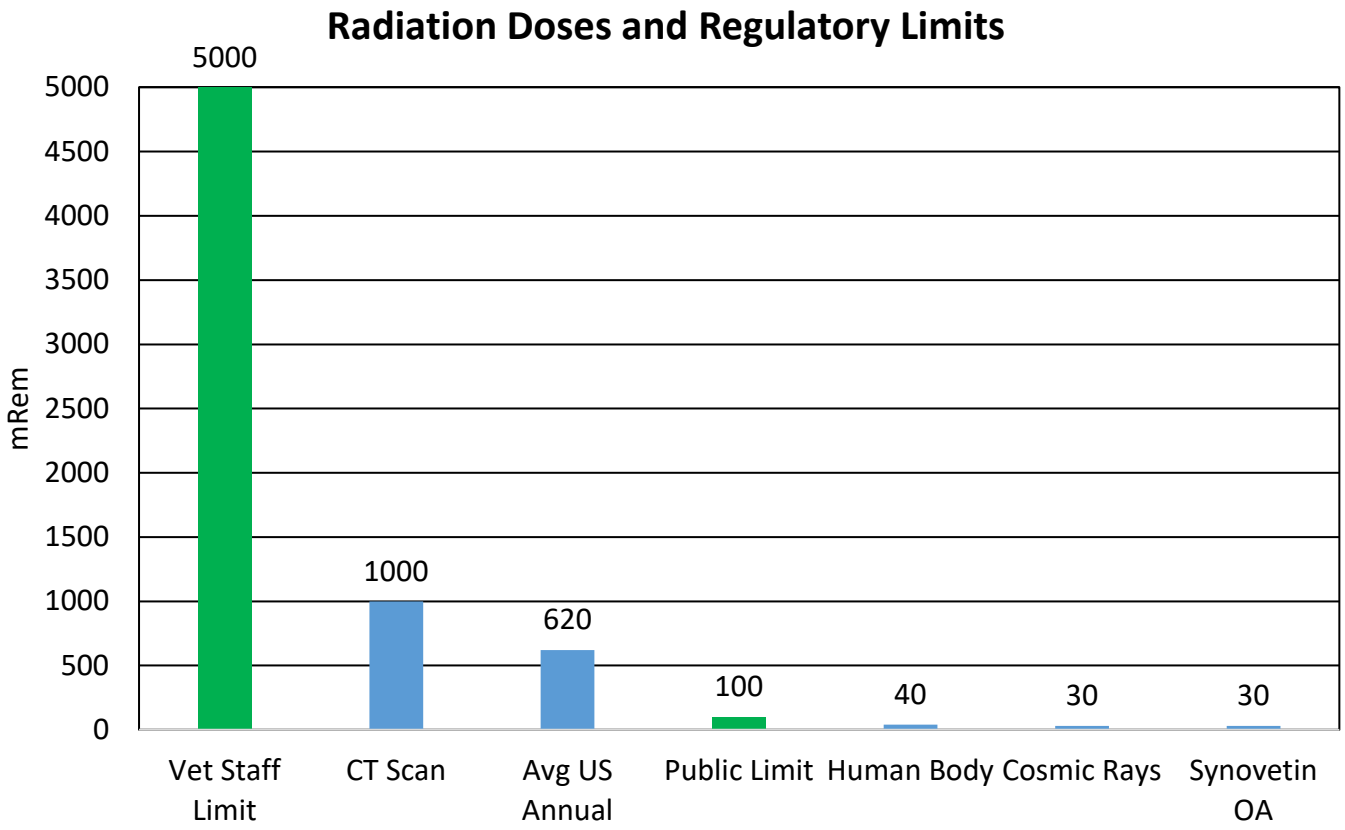
Low, weak energy: Safe for family and other pets



Human Radiotherapy

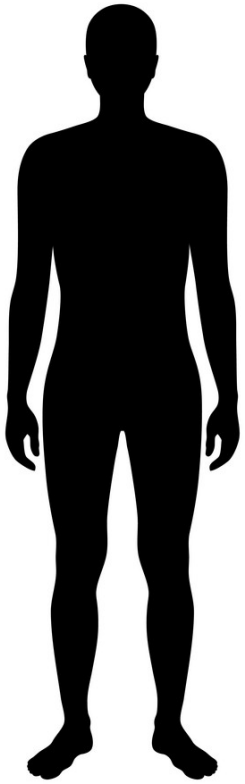
18F-FDG
PET Scan
10-15 mCi

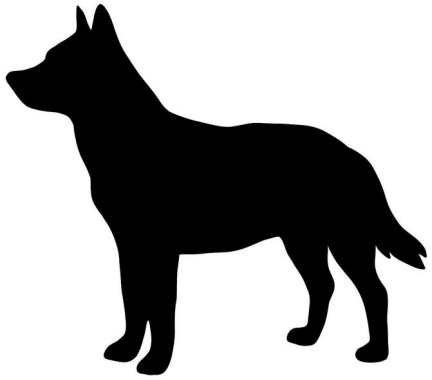
I-131
Hyperthyroidism
30 mCi

Tc-99m
Cardiac Stress Test
30-40 mCi

Pd-103
Prostate Cancer
5 mCi

Ga-67
Lymphoma
9 mCi





Sn-117m
Arthritis
4 mCi (avg)

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Injection Care

- Recover with general population
- Same day go home
- ~4 weeks of limiting contact
  - No sleeping on bed
  - Close contact <15 mins
  - Intermediate contact <4 hours

Instructions following Synovetin OA™ (tin 117m) Canine Arthritis Therapy

Dog's Name: _____ Treatment Date: _____

Total Dose Administered: _____mCi Measured Exposure Rate: ____ mR/h at 1m

Your dog has been treated with Synovetin OA™ (tin-117m) in one or more arthritic joints. Synovetin OA™, a radio-

____ weeks:

- ✓ Do not sleep with the dog or hold the dog in your lap.
- ✓ Each member of the household should limit close contact to _15_ minutes and should limit intermediate contact to _4__ hours. Activities such as walking or playing with your dog can continue as usual.
- ✓ Minimize the time that young children and pregnant women spend in close contact with the dog.
- ✓ Avoid boarding your dog, or traveling with it by air or across any international borders or very large, organized events (professional sporting events, parades, etc.). Keep a copy of this document should any questions arise.
- ✓ Minimize use of public transportation and staying in public accommodations (e.g., hotels). Transport your dog in its carrier as far from passengers as is reasonable and safe for the dog.
- ✓ If your dog needs emergency care, please inform the provider about its treatment with radiotherapy, and to contact (*RSO of facility, at RSO's phone number)* with any questions.

If for any reason your dog dies within four months of treatment and you plan to have it cremated, this may be delayed until the radioactivity has decreased to an appropriate level.

Veterinarian signature: _____Date: _____

I have received this information orally and in writing, and I understand it. I have had the opportunity to ask any questions.

Dog owner signature: _____Date: _____

*Approximately equivalent to 100 days of natural radiation exposure in the United States, or 10 round trip flights from Boston, MA to Los Angeles, CA.

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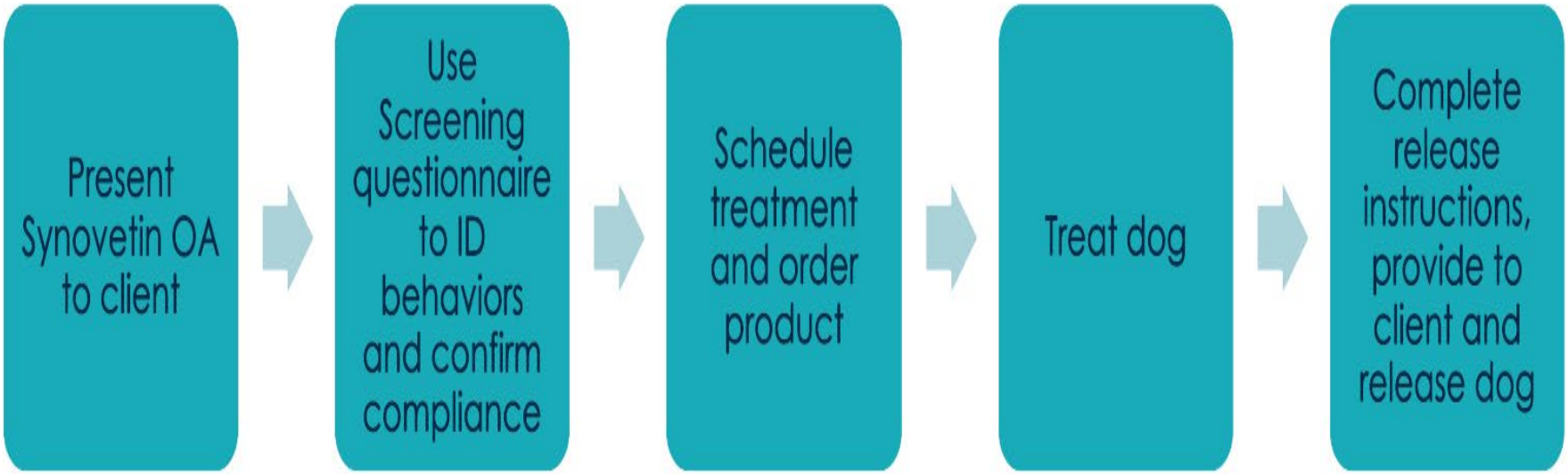
Exposure FYI

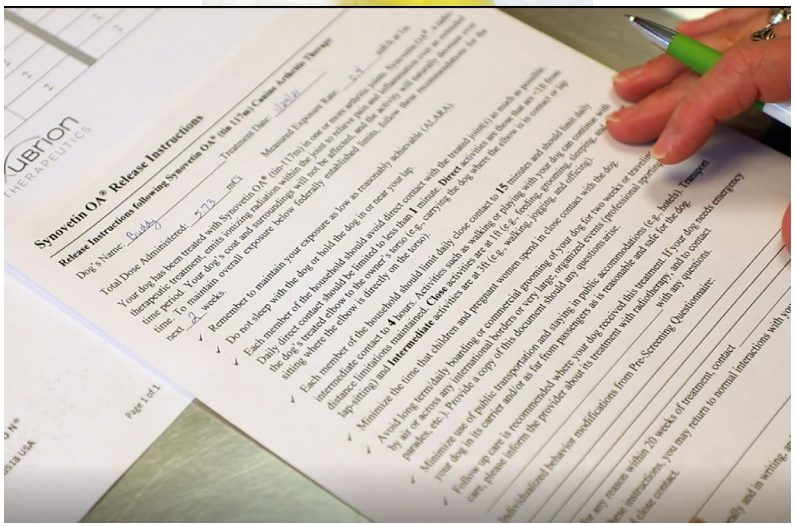
- The maximal expected owner dose with Radionuclide 117m is ~80 mrem
- Humans exposed ~300 mrem of natural background radiation/year

Activity	Radiation dose
2-view chest radiographs	10 mrem
Head CT	200 mrem
Roundtrip flight NY→ SEA	5.6 mrem
100 bananas	1 mrem
Driving 40 miles in a car	10 mrem

The Process


Present Synovetin OA to client
Use Screening questionnaire to ID behaviors and confirm compliance
Schedule treatment and order product
Treat dog
Complete release instructions, provide to client and release dog

Measuring and releasing the dog



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Take Home Notes

- Radionuclide tin-117m (trade name: Synovetin OA)
- Single-dose treatment
- Extended duration of effect: up to a year
- Minimally invasive
- No systemic distribution or side effects
- Safety
- Treatment flexibility
- Annual retreatment

Synovetin OA Pricing

- Veterinary list price: $1,449 for 2 elbows, $949 for 1 elbow
- Pet owner rebates ($200/$75)

- MedVet
  - Approximately 2200-2400 for 1 elbow
  - 2900-3100 for 2 elbows

Typical therapies	Avg. PO cost/yr.
NSAID + glucosamine + Adequan	$1,800+
HA + steroid	$2,200+
PRP	$3,000+
Bi-lateral arthroscopy	$4,000+

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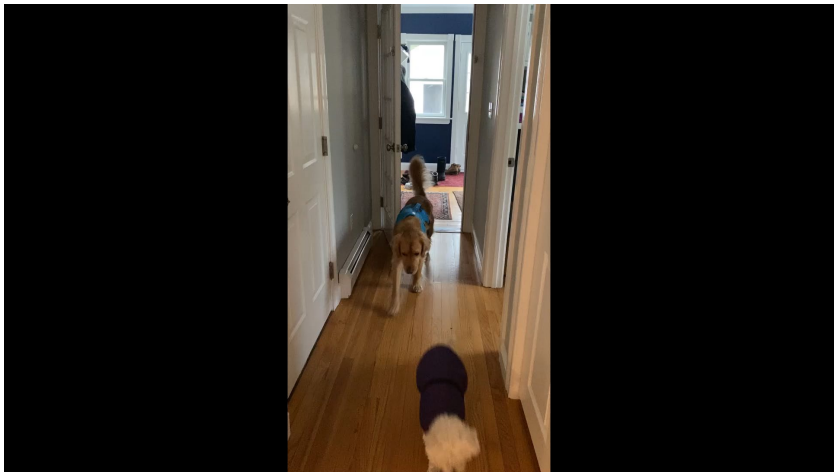
Treatment Experiences



Napoleon

4-year-old English Lab

Before Synovetin OA Treatment

Confirmed elbow OA, primary treatment: NSAIDs

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EXUBRION THERAPEUTICS

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Long lasting
Safe
Convenient

www.synovetin.com

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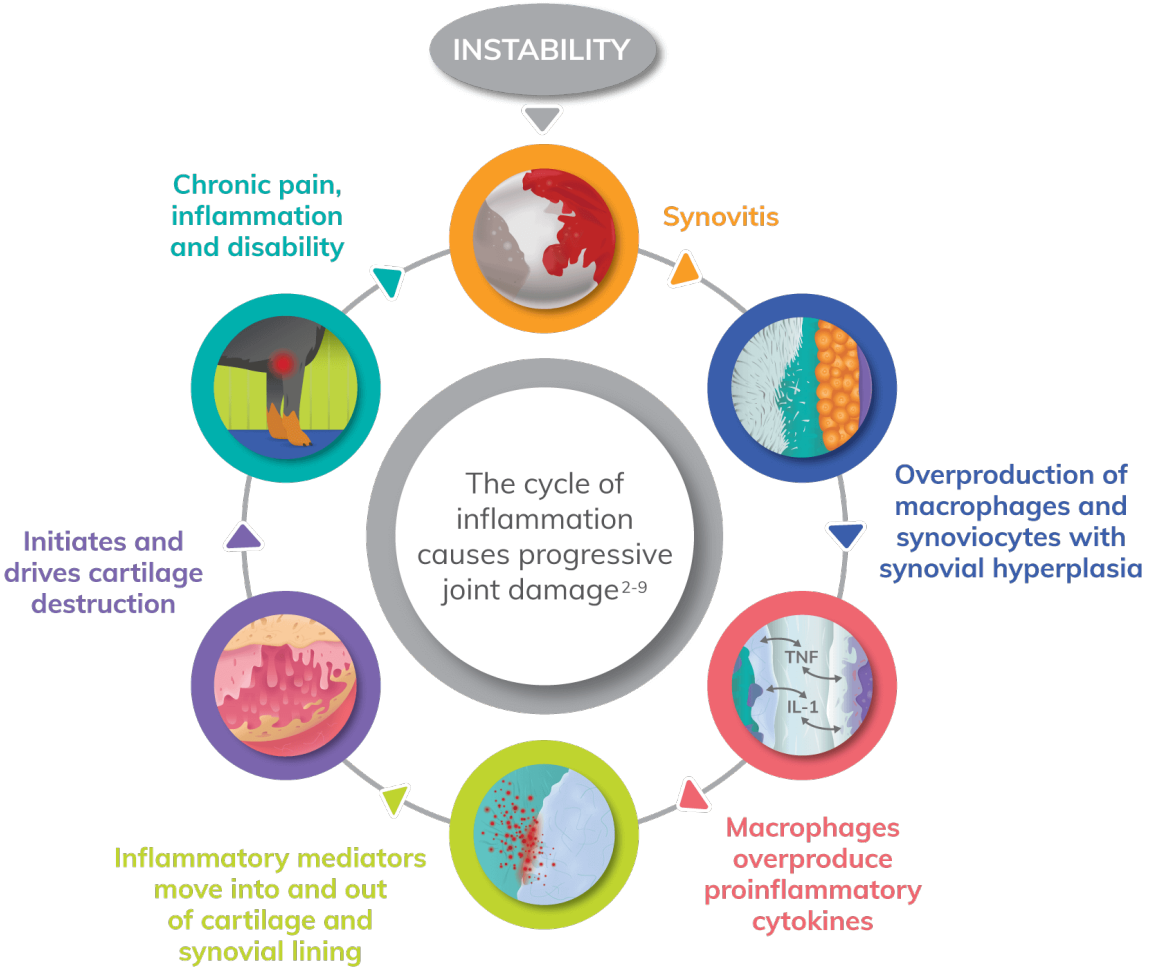
Questions?

- Long term clinical outcome?
- Clinical outcome in other joints
- Insurance?



Thanks to Kevin Benjamino, Eric Schreiber, Haley Mascellino

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MYKONOS
Heather & Connie Hopkins
Kansas City, MO
Synovetin OA

MedVet

Mykonos Experience

Synovetin OA™

- ✓ **Mykonos, 1.5 year old, castrated male, 88 lb. German Shephard, bilateral ununited anconeal processes.**
  - ✓ **Right elbow injected with label dose 10/14/15**
  - ✓ **Left elbow injected with label dose 9/20/16**

cBPI scoring	Baseline	1 mos.	3 mos.	6 mos.	9 mos.	Baseline^2	1 mos.	3 mos.
Date	10/13/15	11/10/15	1/7/16	4/1/16	7/7/16	9/19/16	10/26/16	12/15/16
Pain Severity Score (Q 1-4)	6.25	2.00	0.75	0.00	0.00	6.00	0.00	0.00
Pain Interference Score (Q 5-10)	2.17	0.83	0.00	0.33	0.00	7.17	0.00	0.00
Quality of Life Score (Q 11)	Good	Very Good	Very Good	Excellent	Excellent	Poor	Excellent	Excellent

Baseline prior to left elbow injected
Baseline^2 prior to right elbow injected

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Mykonos Experience

Synovetin OA™

- ✓ **Mykonos, 1.5 year old, castrated male, 88 lb. German Shephard, bilateral ununited anconeal processes.**
  - ✓ **Right elbow injected with label dose 10/14/15**
  - ✓ **Left elbow injected with label dose 9/20/16**
  - ✓ **Both elbows injected with label dose 12/18/17**

	6 mos.	9 mos.	12 mos.	Baseline[3]	3 mos.	6 mos.	9 mos.	12 mos.
Date	3/23/17	6/22/17	9/21/17	12/17/17	5/4/18	7/6/18	9/21/18	12/30/18
Pain Severity Score (Q 1-4)	0.00	0.00	0.00	0.75	0.00	0.00	0.00	0.00
Pain Interference Score (Q 5-10)	0.00	0.00	0.00	0.67	0.00	0.00	0.00	0.00
Quality of Life Score (Q 11)	Excellent	Excellent	Excellent	Very Good	Excellent	Excellent	Excellent	Excellent

Baseline[3] prior to both elbows injected

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Thank you!

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Leading Specialty Healthcare for Pets