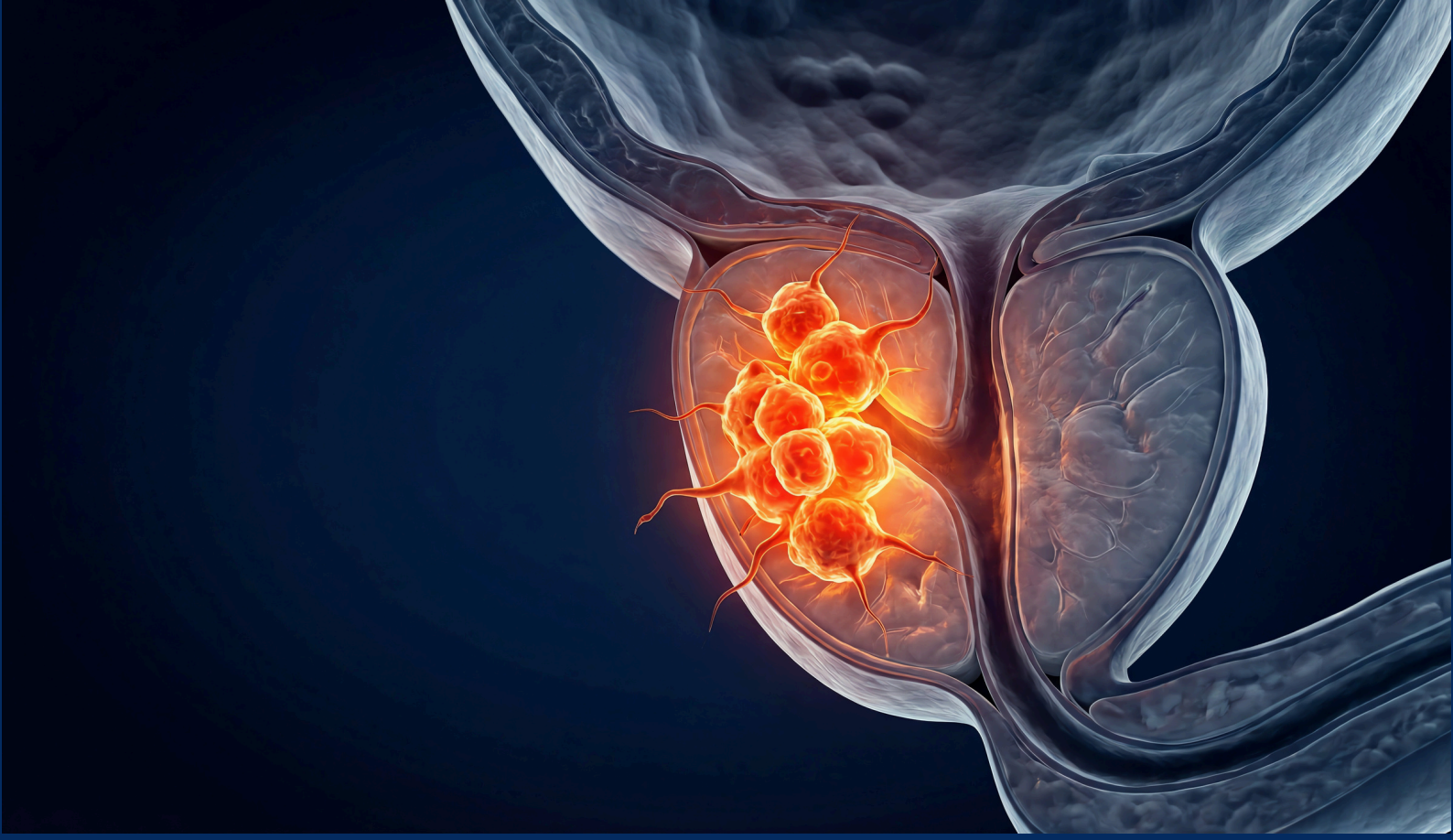
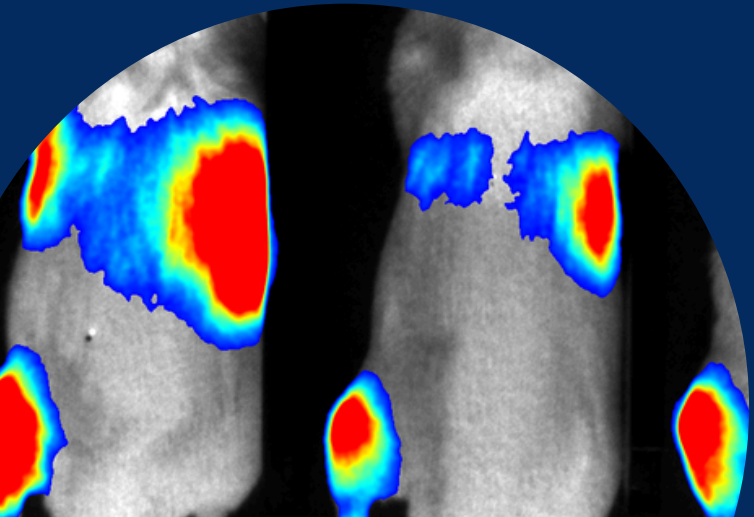


Case Study

Modeling and Characterizing Metastatic Prostate Cancer: Inducing and Longitudinally Tracking Disease Progression

Two methods for reproducing metastatic dissemination in vivo, with longitudinal monitoring and characterization of cancer spread via preclinical imaging.



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Over 30 Years of Experience in Preclinical Research

Introduction

Prostate cancer was globally responsible for more than 420,000 deaths in 2024, accounting for 14.6% of all incidences of male cancer and 7.7% of male cancer mortalities. Both incidences of and mortalities arising from prostate cancer are currently predicted to double by 2050, according to the Global Cancer Observatory. Metastatic progression, mainly in lymph nodes, bones, liver, and lungs, remains the major cause of prostate cancer mortality.

A recent study at Oncodesign Services, incorporating results from studies conducted for Oncodesign Precision Medicine, explored how different injection routes and longitudinal bioluminescence imaging can be used to establish and characterize metastatic prostate cancer in preclinical models. The findings highlight a broader consideration for preclinical research: when studying metastatic cancer, understanding where secondary tumors develop may not fully capture how the disease progresses.

Why metastatic prostate cancer is difficult to model

There are few preclinical models available that are capable of recapitulating advanced stages of metastatic cancer and reproducing the associated dissemination patterns of the disease, increasing the difficulty of investigating metastasis in a preclinical setting.

When metastatic disease can be established in a research model, an important hurdle to overcome is successfully tracking disease progression over time. Endpoint analysis can reveal where metastases have developed but reveals much less about when dissemination occurred, how rapidly disease progressed, or how patterns of metastasis differed between individual models.

Lymph nodes and bone are the predominant sites of prostate cancer metastasis, but advanced disease can also spread to visceral organs, including the liver and lungs. Reproducing these patterns of dissemination in preclinical models is complex.

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Subcutaneous tumor models provide valuable tools for evaluating anticancer activity, but more specialized models are required when the research objective extends beyond primary tumor growth. Researchers also need appropriate methods to characterize disease progression:

- When did dissemination become detectable?
- Which anatomical sites were affected?
- How rapidly did metastatic burden increase?
- How consistent was progression between individual animals?

Answering these questions requires the ability to follow disease longitudinally.

Comparing two approaches to model development

Researchers at Oncodesign Services investigated the establishment of liver and lung metastasis in immunodeficient male mice using 22Rv1-Luc-mCherry prostate cancer cells delivered via intra-tibial or intra-arterial injection.

Expression of luciferase enabled longitudinal monitoring of tumor growth via bioluminescence imaging, while mCherry expression provided an additional fluorescent marker for metastatic lesion characterization via fluorescence imaging. When imaging is used to monitor disease progression in this way, scans are able to discern and capture the location and cell density of lesions over time.

By following progression longitudinally in this study, researchers were able to characterize the differences in the kinetic distribution and progression of disease between the two delivery approaches.

22Rv1-Luc-mCherry

The 22Rv1 tumor cell line is a human prostate carcinoma cell line (American Type Culture Collection, USA) derived from a xenograft that was serially propagated in mice after castration-induced regression and relapse of the parental, androgen-dependent CWR22 xenograft.

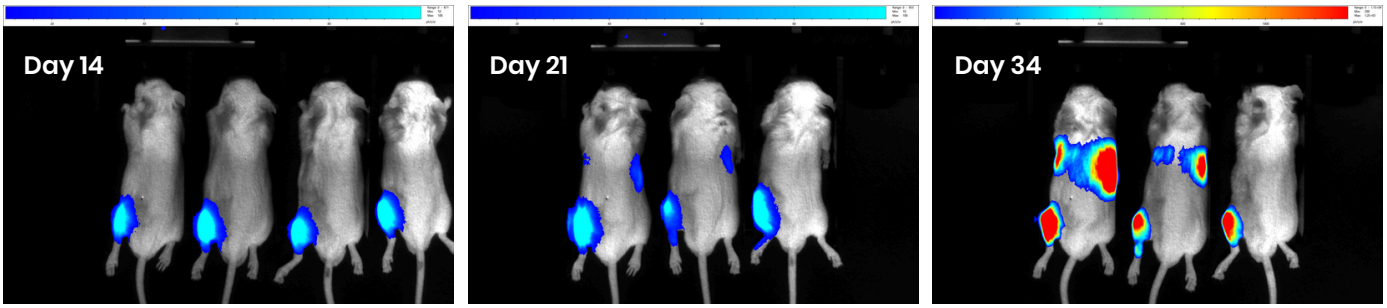
The cell line was modified using recombinant lentivirus (pLV[Exp] mCherry:T2A:PuroEF1A>Luciferase (Vector ID: VB900086-1810hym)). Cells were then cultured on puromycin pressure to keep only 22Rv1 tumor cells expressing luciferase and mCherry to follow tumor progression in vivo using in vivo bioluminescence imaging and/or to perform in vitro and ex vivo analysis.

Disease dissemination: Intra-tibial injection

Intra-tibial injection was used to establish an initial tumor within the bone, mimicking metastatic spread into bone.

For the first 21 days following injection, bioluminescence signals remained localized to the tibia. From day 28 onwards, additional signals became detectable at distant anatomical sites.

Further investigation also identified metastatic dissemination to the liver and lungs.

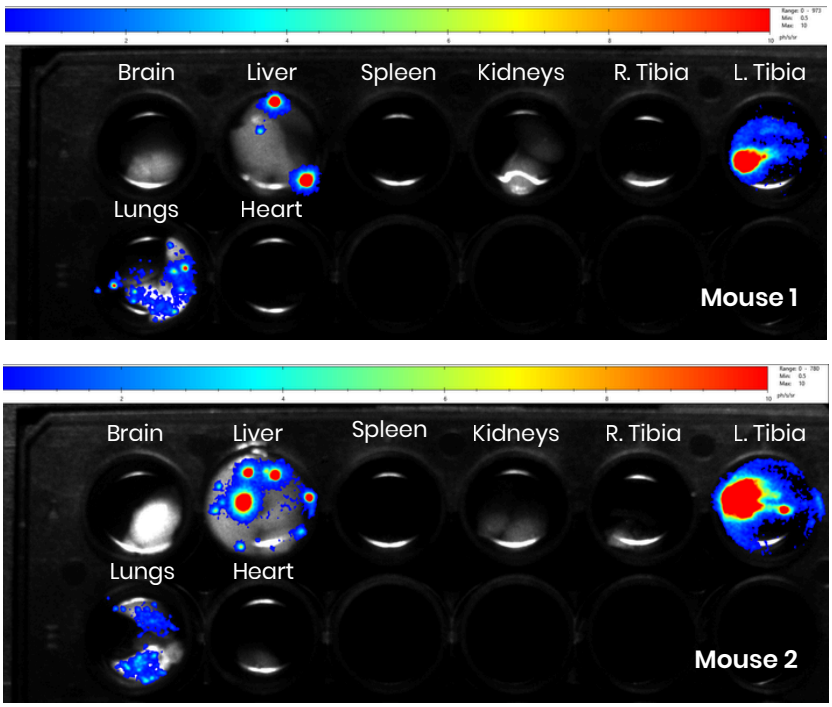


Results from longitudinal bioluminescence imaging of the intra-tibial injection group, showing signals localized to the tibia until day 21, followed by detectable distant dissemination to the liver and lungs on day 34. An alternative scale from days 7 to 21 allows early visualization of lower signals.

An endpoint assessment demonstrated the presence of tumor cells at multiple anatomical sites. Repeated imaging reveals more of the trajectory between injection and endpoint, providing information about when the pattern of disease begins to change.

In ex vivo bioluminescence images of organs after intra-tibial injection at day 28, important signals were observed in left tibia (site of injection) and in the liver. Weaker signal was also observed in the lungs.

For researchers evaluating new therapeutics, understanding this trajectory can be important when determining the appropriate window for intervention and assessing treatment response.

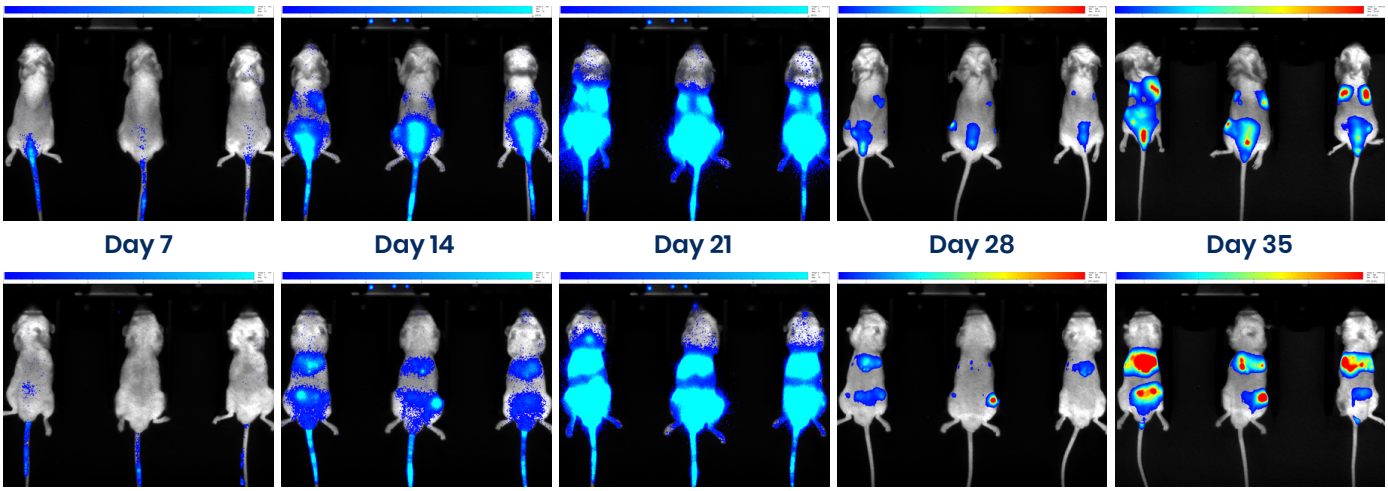


Ex vivo BLI endpoint readouts of organs harvested from two mice from the intra-tibial group at day 28 confirm metastatic dissemination to organs. The strongest signal is observed at the injection site (bone - left tibia), with significant signal observed in the liver and weaker signal present in the lungs.

Disease dissemination: Intra-arterial injection

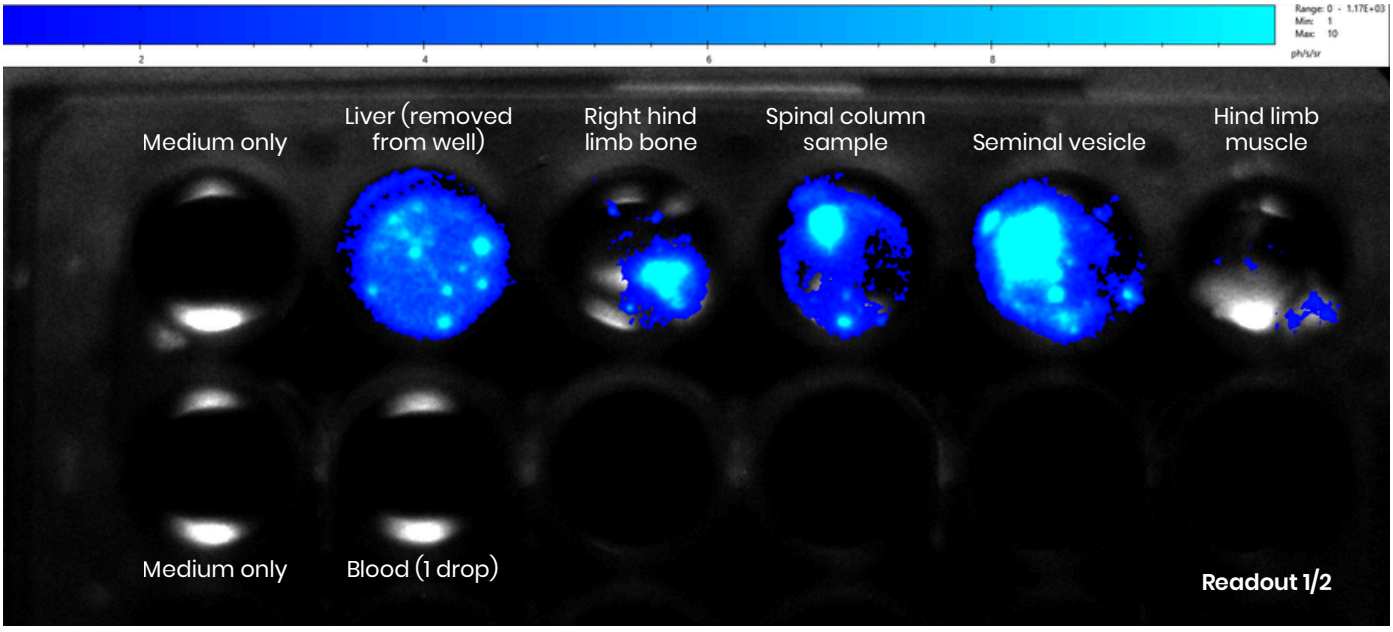
The intra-arterial approach produced a different disease trajectory.

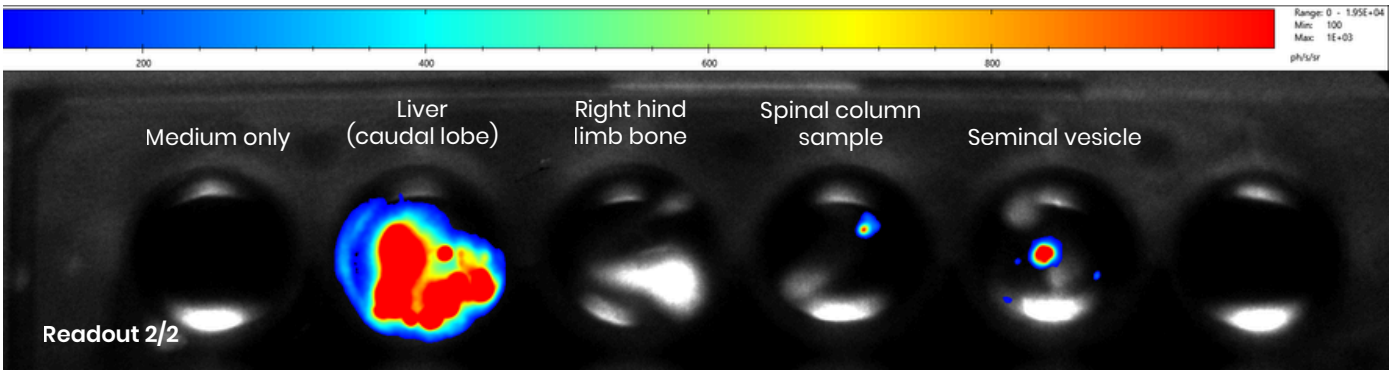
Following injection, bioluminescence signals were initially observed in the bones. Over time, increasingly prominent signals developed in the liver.



Disease evolution following intra-arterial injection. Mice were imaged back (upper panel) and belly (lower panel) with two scales of signal to detect (earlier) weaker and (later) stronger signals. Change of scale was done between day 21 and day 28 to allow better visualization of signal. Back imaging showed early signal in back bone and limb bone from day 7 to day 28. At day 35, signal appeared in the liver. Belly imaging showed more hepatic signal compared to bone signals.

Ex vivo imaging at the end of the study confirmed the presence and anatomical localization of metastatic lesions.





Ex vivo bioluminescence images of organs after intra-arterial injection at day 42. Important signals were observed in the liver. Signals were also observed in hind limb bone, spinal column and seminal vesicle.

The comparison between the two approaches highlights an important consideration in metastatic model development: The route used to introduce tumor cells is not a technical detail. It can influence the pattern and timing of anatomical distribution of disease.

The role of preclinical imaging

The value of longitudinal imaging extends beyond visualizing disease progression, changing the nature of the information available during the experiment. Endpoint analysis can establish the final distribution of disease. Repeated non-invasive imaging throughout a study provides additional information about how the disease developed, with implications for several aspects of study design:

Treatment initiation

The timing of therapeutic intervention can significantly influence the outcome of an efficacy study. Longitudinal imaging can help identify intervention points based on observed disease progression rather than study duration alone.

Assessment of treatment response

Changes at a primary tumor site may not fully reflect therapeutic activity against metastatic disease. Imaging can enable disease burden to be followed across different anatomical locations.

Cohort allocation

Metastatic burden and distribution can vary between individual models. Imaging before treatment allocation can provide additional information to support balanced experimental groups.

Reduction and refinement

Repeated non-invasive measurements in the same animal can reduce reliance on separate cohorts at multiple timepoints, while generating longitudinal data on individual disease trajectories and supporting more refined study designs.

Repeated measurements within the same models also provide information about the kinetics of progression that cannot be generated through endpoint assessment alone. This can increase the scientific information obtained from a study while supporting the refinement of experimental design and animal use.

Conclusions

This study demonstrates how these preclinical models can reproduce the clinical scenario following surgical resection of the primary tumor, where relapse may arise from pre-existing micrometastases that were undetectable at the time of surgery.

There is no single preclinical model capable of answering every question about metastatic prostate cancer. The intra-tibial and intra-arterial approaches examined in this study generated different patterns of disease progression; however, neither is inherently a universally superior model. The experimental relevance of each model depends on the therapeutic mechanism, disease setting, expected treatment response, and endpoints required.

Study results strongly reinforce that model selection should begin with the specific biological and experimental question, such as →

- When did dissemination become detectable?
- Which anatomical sites were affected?
- How rapidly did metastatic burden increase?
- How consistent was progression between individual animals?

Different research questions may require different experimental approaches. For this reason, model development and study design should not be considered separately.

What can researchers take from this study?

Injection route can shape disease progression
Different experimental approaches produced distinct patterns of metastatic dissemination and should be selected according to the research question.

Endpoint data provide a partial picture
Longitudinal imaging can reveal when and how disease progresses between tumor establishment and final assessment.

Model selection should follow experimental objective
Disease setting, mechanism of action, expected response, and required endpoints should inform the experimental approach.

Imaging can inform study design as well as efficacy assessment
Longitudinal monitoring can support decisions around treatment initiation, cohort allocation, disease progression, and response evaluation.

Metastatic disease is dynamic by nature. The preclinical approaches used to study it should ideally enable researchers to capture more of this systemic complexity.

By combining metastatic model development with longitudinal imaging, researchers can move beyond asking whether disease has progressed and begin investigating the more informative questions of where, when, and how that progression occurs.

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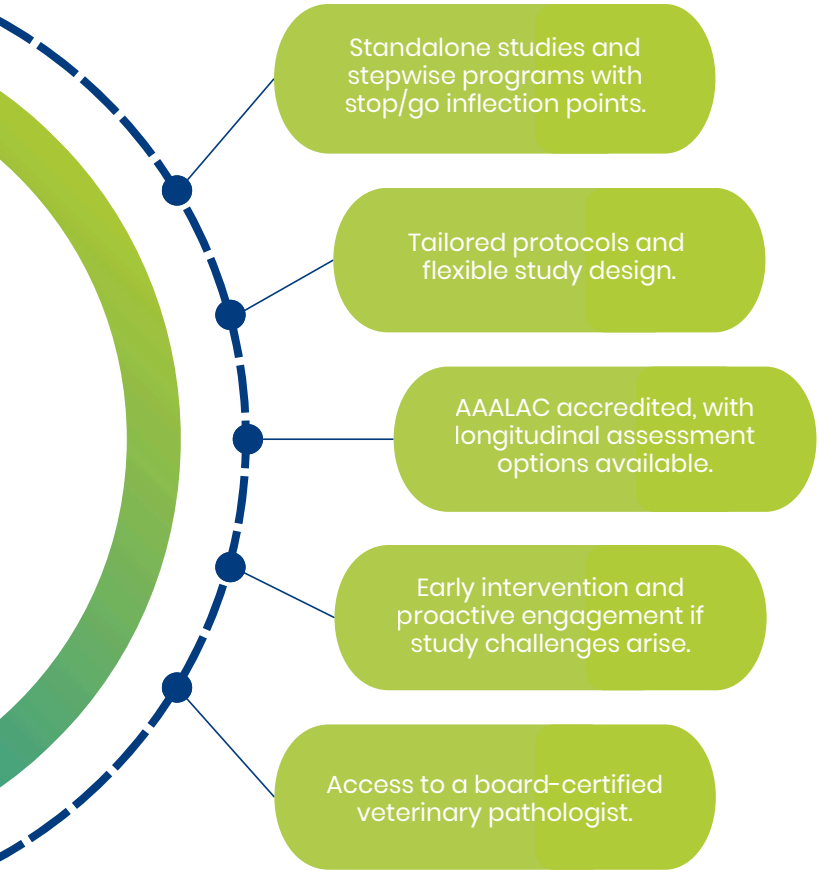

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