A growing body of evidence...

There is a growing body of evidence that low stores of vitamin D are associated with a wide range of diseases in dogs and cats:

- Cancer (2,5,8,9,11,12,13,20,26,27,56)
- Chronic Enteropathy (4,12,17,19,29,36,45,54)
- Heart disease (10,18,48)
- Atopic dermatitis (7,32,49,50)
- Kidney disease (1,2,25,26,52)
- Hyperparathyroidism (2)
- Immune mediated disease (22,31,44,50)
- Infection (6,9,16,28,23,40,42,53)
- Pancreatitis (24,33,41)
- Feline tooth resorption (3)
- Hospital Mortality (14,35)
- Toxicity (30,46)
- Mechanism of Action (8,20,36,37,38,39,43,44,47,49,51,55,56)
- Dietary (1315,21,30,34,46)

Vitamin D is the precursor of the powerful steroid hormone calcitriol. Aside from its regulatory role on calcium and phosphate homeostasis, vitamin D has a strong immune-modulatory role triggered when bound with vitamin D receptor (VDR), a member of the nuclear-receptor superfamily which includes corticosteroids.

Vitamin D insufficiency has been linked to abnormal calcium management and secondary hyperparathyroidism as well as immune dysfunction. Consistent with the human literature, vitamin D insufficiency has been linked to many diseases in companion animals.

Diet is the primary source of vitamin D in the form of 25 hydroxyvitamin D (25vitD) acquired from the protein source in food. Commercial manufacturers supplement with vitamin D3 however, in most instances, it fails to make up for insufficiencies in the commercial processing of dog and cat food.
A growing body of evidence...

Studies Conclude 25vitD Levels below 40ng/mL Result in Adverse Outcomes

**Cancer**
It has been reported that dogs and cats with lymphoma (2,12), mast cell tumors (5), hemangiosarcoma, carcinoma, histiocytic sarcoma, and other cancers (11,12,13) all have 25vitD values below 40 ng/mL. The relative risk of having cancer increases to almost 4x when 25vitD values are below 40 ng/mL.

**Chronic Enteropathy**
Disease severity and the incidence of chronic enteropathy (CE) in both cats and dogs increases substantially when 25vitD values fall below 40 ng/mL (4,12). In CE, survivors vs non-survivors can be separated when 25vitD values fall below 30ng/mL (16,19,29,36).

**Heart Disease**
Congestive heart disease is more prevalent in dogs with 25vitD values below 40ng/mL and there is a 2.6x increase in cardiovascular events (10). Heart remodeling in chronic valvular heart disease worsens as 25vitD values fall below 30 ng/mL (18).

**Chronic Kidney Disease**
Studies show acute and chronic kidney disease is more prevalent in dogs with 25vitD values below 40 ng/mL (1,2). As 25vitD values fall below 40ng/mL, creatinine increases dramatically (25).

**Hospital Mortality**
Hospitalized cats with 25vitD levels below 40 ng/mL have an 8x higher incidence of dying (14) and hospitalized dogs with 25vitD levels below 33ng/mL have a 7x higher incidence of dying (35).

**Calcitriol Drops**
25vitD is the substrate for the enzymatic conversion to the active hormone calcitriol. When 25vitD values fall below 40 ng/mL, there is difficulty in maintaining proper calcitriol levels (1).

As a result, ionized calcium can fall below the reference interval (4,33). Maintaining proper ionized calcium levels is vital for muscle and nerve function.

VDI has concluded that the body of evidence supports a high risk of disease and/or death when 25vitD levels are below 40 ng/mL and therefore defines this as “DEFICIENCY”.

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VDI Laboratory, LLC
A growing body of evidence...

Defining Vitamin D SUFFICIENCY
25vitD sufficiency is defined not only as the proper level for the management of calcium homeostasis, but also the innate immune response. It comes from two methods; surrogate biomarkers and clinical evidence.

Surrogate Biomarkers
In a major study (13) that defined vitamin D sufficiency [modeled after a human study (i)], four surrogate biomarkers were chosen to define the proper level of 25vitD in dogs. These biomarkers were intact parathyroid hormone (iPTH), calcium, phosphorous, and C-reactive protein (CRP).

Vitamin D and PTH
Through negative feedback, the parathyroid gland senses ionized calcium levels and adjusts PTH levels to regulate the enzymatic conversion of 25vitD to calcitriol facilitating intestinal absorption of calcium. Further, PTH activates osteoclasts to increase calcium release from the bone. As 25vitD levels increase, iPTH decreases. When iPTH plateaus, 25vitD sufficiency has been attained. The study found this occurred at 100 ng/mL of 25vitD.

Vitamin D and Calcium/Phosphorous
The maintenance of proper serum calcium and phosphorus is critical for proper muscle and nerve function. Calcium and phosphorous levels should be stable and variability minimal. The study found the level was reached at 100 ng/mL of 25vitD.

Vitamin D and Inflammation
Vitamin D (25vitD & calcitriol) and its receptor (VDR) are found on a variety of cells (eg, mast, WBC) and tissues (eg, skin, intestines) (36) regulating gene transcription and the innate immune response. Studies (13,37,38,39) have shown vitamin D influences the inflammatory cascade involved in the production of acute phase proteins (APP). In dogs, CRP is the major APP. The study (13) found CRP (inflammation) drops when 25vitD levels reach 100ng/mL.

Clinical Evidence
The relative risk of developing cancer drops as 25vitD levels approach 100ng/mL and becomes beneficial with values above 100 ng/mL (13).

In dogs with CKD, those whose 25vitD levels approach 100 ng/mL had the lowest creatinine levels (25).

In a vitamin D interventional study on dogs with atopic dermatitis, those with 25vitD levels within the range of 100-150 ng/mL saw significant improvement in both pruritus and CADESI scores (31).

Inflammation markers (neut ct, mono ct, IL-2, IL-6, IL-8, TNF-alpha) all significantly drop in CE dogs as 25vitD levels approach 100 ng/mL. The duodenal histopathology score also significantly improves with 25vitD levels approaching 100 ng/mL (19).

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25vitD Status in Dogs and Cats
Diet is the primary source for vitamin D in dogs and cats whether it is D3 additives to the food or within the protein source primarily as 25vitD. Many factors affect vitamin D status which includes:

- **Food**
  - Certain manufacturers of food can have profound differences in 25vitD status (15).
- **Age**
  - As animals get older their ability to absorb vitamin D diminishes (VDI internal data).
- **Neuter Status**
  - Male neutered dogs have 27% less 25vitD than intact males; female spaying drops by 9% (15).
- **Disease**
  - Diseases affecting the GI tract have the greatest impact on vitamin D absorption (412,16,19,29,36).
- **Medication**
  - COX2 inhibitors (e.g., meloxicam) can cause drops of up to 50% (VDI internal data).
  - Corticosteroids upregulate the consumption of vitamin D (VDI internal data).

Unsupplemented Distribution
The incidence of 25vitD deficiency, as defined as <40ng/mL, is 11% in dogs and 22% in cats.

The incidence of 25vitD sufficiency, as defined as >100ng/mL, is 21% in dogs and 14% in cats.

Vitamin D Insufficiency
Vitamin D insufficiency is easy to test and correct with inexpensive D3 supplementation. The amount of D3 required depends upon the degree of insufficiency (determined by testing), the patient's species, weight, age, intact status, and other factors. VDI has developed a D3 dosing system that is tailored to each pet.

Testing is simple and cost effective using VDI's dried serum methodology. The patient's serum is applied to a card and simply mailed by common carrier. The card easily crosses international borders without custom declarations.

Dosing information is provided on the report with a pet-parent friendly information sheet detailing the result and D3 dosing required for their cat or dog.
Finally, there is a blood test for early cancer detection in dogs

"Early detection and treatment are the best ways to manage cancer in pets... cancer is frequently treatable and early diagnosis will aid your veterinarian in delivering the best care possible."

- American Veterinary Medical Association

What is cancer screening?

Just like in people, cancer screening should be an important part of preventive care in dogs; the goal is to look for cancer when your pet is feeling well, before they start to show any clinical signs. During wellness visits, your veterinarian may look for early signs of cancer in your dog by performing a thorough physical exam and asking you about any concerning observations. Your veterinarian may also perform routine blood and imaging tests, and may recommend OncoK9 - a new blood test that could detect cancer before your dog shows any clinical signs.

What is OncoK9?

The OncoK9 liquid biopsy test uses a simple blood draw to detect abnormal DNA released into circulation by cancer cells.

- **SIMPLE BLOOD DRAW**
  Your veterinarian will collect a blood sample from your dog.

- **MULTI-CANCER COVERAGE**
  OncoK9 can detect 30 different types of cancer, including eight of the most common cancers in dogs.

- **CUTTING-EDGE TECHNOLOGY**
  OncoK9 uses state-of-the-art next-generation sequencing (NGS) technology to detect changes in DNA that are indicative of cancer.

- **EARLY DETECTION**
  OncoK9 may help detect cancer early, when your dog still looks healthy and has the best chance of defeating the disease.

- **CLINICALLY VALIDATED**
  OncoK9 was clinically validated with the largest clinical study of its kind.

Cancer Is by Far the #1 Cause of Death in Dogs

Defeating cancer starts with knowing your dog has it.
Which dogs may benefit from **cancer screening** using OncoK9®?

**All Dogs Age 7 and Older**
Older dogs are at higher risk of cancer, regardless of breed. Consider adding OncoK9 to their routine wellness exams.

![Graph showing annual incidence of cancer (per 100,000 dogs) with age]

9x Higher Risk of Cancer Over Age 7

&

**Younger Dogs from Breeds at Higher Risk of Cancer**
Certain breeds, shown to the right, have a higher lifetime risk of cancer and/or higher risk of developing cancer earlier in life.

![Images of dogs representing different breeds]

- **Common Breeds**
  - Beagle: 7 years
  - Basset Hound: 7 years
  - Boxer: 4 years
  - Flat-Coated Retriever: 7 years
  - French Bulldog: 6 years
  - German Shepherd: 7 years
  - Golden Retriever: 6 years
  - Labrador Retriever: 7 years
  - Rhodesian Ridgeback: 6 years
  - Rottweiler: 6 years
  - Siberian Husky: 7 years

- **Giant Breeds**
  - Great Dane: 4 years
  - Irish Wolfhound: 4 years
  - Mastiff: 4 years
  - Scottish Deerhound: 6 years

**When should I start screening my dog?**
Scan this QR code to access the OncoK9 Cancer SAFE™ Tool to find out the recommended age to start cancer screening for your dog, or visit cancersafe.petdx.com.

Ask your veterinarian about **OncoK9® today**

**OncoK9 - Disclosures & Risks**
OncoK9 requires a blood collection performed under the care of a licensed veterinarian, and test results are returned to the veterinarian for communication to the pet owner. As with any laboratory test, OncoK9 results should be interpreted by a veterinarian in the context of each patient's medical history and clinical presentation. Test failures and false positive or false negative results may occur. To review OncoK9 test limitations and risks, please visit: onco9.info/disclosures.