

SDMA impacts how veterinarians diagnose and manage kidney disease in dogs and cats



Introduction

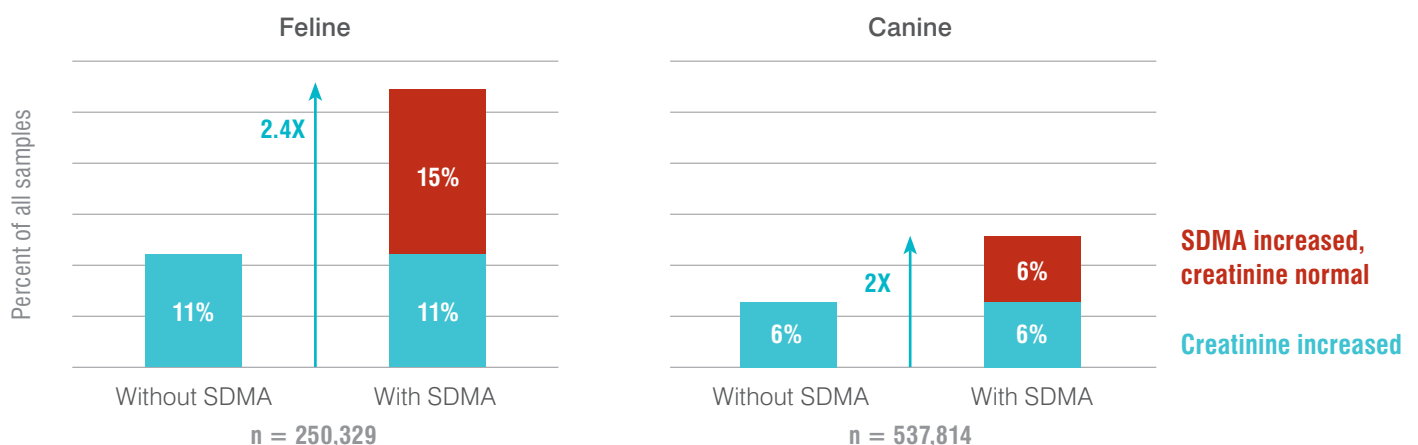
The renal biomarker symmetric dimethylarginine (SDMA) was introduced in July 2015, and since that time, more than 12,000 clinics have submitted over one million blood samples to IDEXX Reference Laboratories for SDMA testing. SDMA has been shown in controlled studies in dogs and cats to be a more sensitive biomarker of renal function than creatinine^{1,2,3} and has recently been added to the International Renal Interest Society (IRIS) Chronic Kidney Disease (CKD) Staging Guidelines.⁴ Results from the tests submitted to IDEXX Reference Laboratories to date have shown that SDMA has potentially helped veterinarians detect early-stage kidney disease in over 2 times the number of cats and dogs than traditional methods.⁵ Not surprisingly, SDMA is increased more frequently as pets progress in age, providing solid evidence that as dogs and cats age, they are more likely to develop chronic kidney disease.

SDMA data supports that kidney disease is two times more common than previously reported

CKD is a common disease in dogs and cats. Previous studies have found that 1 in 3 cats and 1 in 10 dogs are likely to develop kidney disease in their lifetime.^{6,7} However, these studies used azotemia to make the diagnosis of kidney disease and likely missed nonazotemic dogs and cats with CKD, particularly those with IRIS CKD Stage 1 or Stage 2 disease. In a recent study in cats, the prevalence of CKD was even higher than previously believed, with 50% of cats of all ages and as high as 80.9% of cats 15 years of age and older diagnosed with CKD.⁸ In this study performed at North Carolina State University, cats were diagnosed with CKD based on results of complete blood count (CBC), serum chemistry, urinalysis, and radiographic determination of degenerative kidney changes and kidney size. They were then staged per the IRIS CKD Staging Guidelines. The majority of the cats (>90%) had IRIS CKD Stage 1 or Stage 2 disease, which highlights that, until now, CKD has been underrecognized.

SDMA now provides practitioners a better tool to identify these pets with CKD before azotemia develops. At this time, IDEXX has one of the largest databases on the prevalence of kidney disease, with over one million SDMA results generated to date across cats and dogs of all ages and breeds. Figure 1 shows that 11% of cats and 6% of dogs* had an increase in creatinine above the reference interval.[†] However, there is an additional 15% of cats and 6% of dogs identified to have increased SDMA with a normal creatinine. Numerous studies to date have shown that SDMA can detect kidney disease when creatinine is normal because it can identify disease earlier^{1,2,3} and because it is not negatively impacted by muscle mass.^{9,10} These findings suggest that by using SDMA, veterinarians have the potential opportunity to diagnose kidney disease 2.4 times more in cats and 2.0 times more in dogs, compared to traditional methods.

Figure 1. With SDMA, over 2 times the number of pets could be diagnosed with kidney disease.



SDMA is increased more frequently as pets progress in age

It has long been recognized that the prevalence of CKD increases with increasing age. In figures 2 and 3, it is clear that SDMA is increased more frequently as pets progress in age (for complete data, see tables in the appendix). This new data provides strong evidence that the prevalence of kidney disease in older pets is much higher than previously reported, and it also provides further insight as to its prevalence by age.

Figure 2. Prevalence of kidney disease increases with age in cats (n = 250,329).

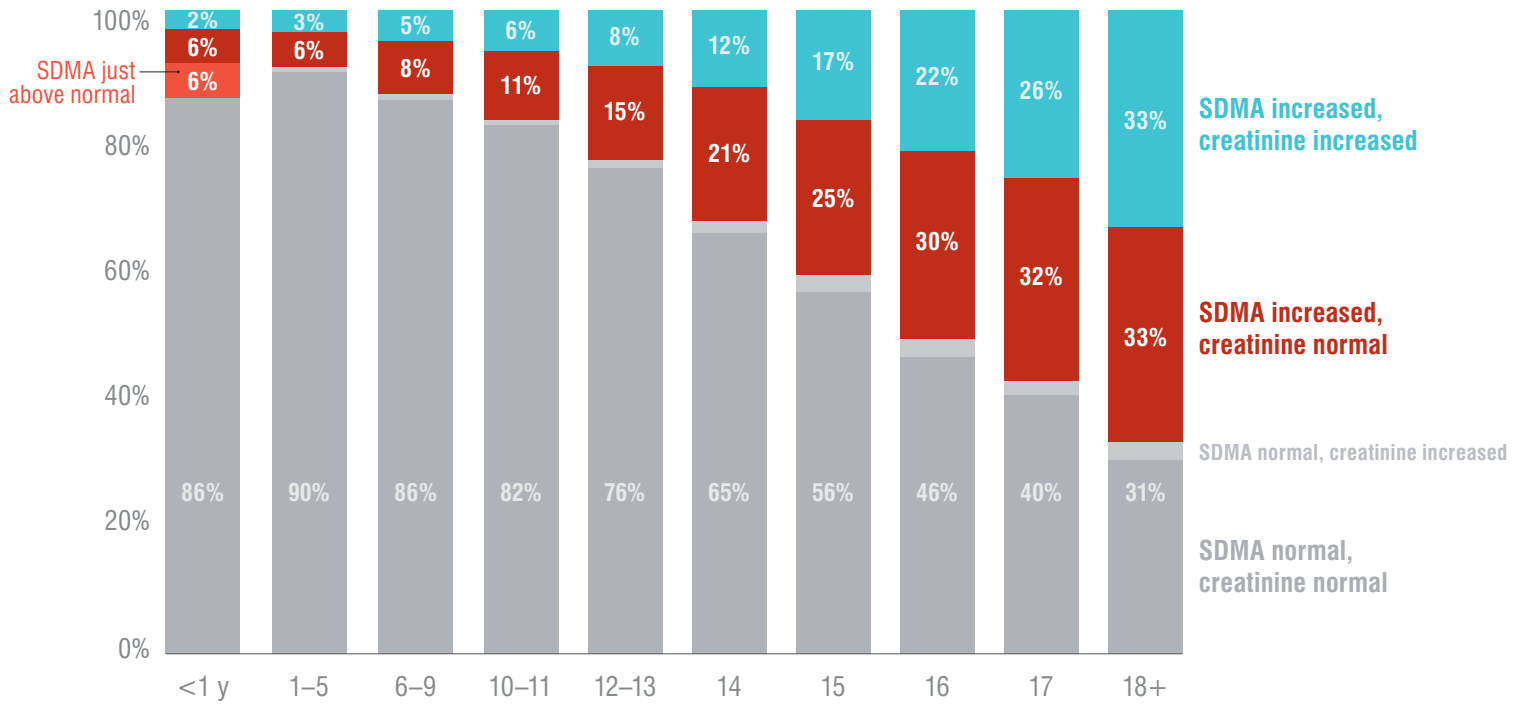
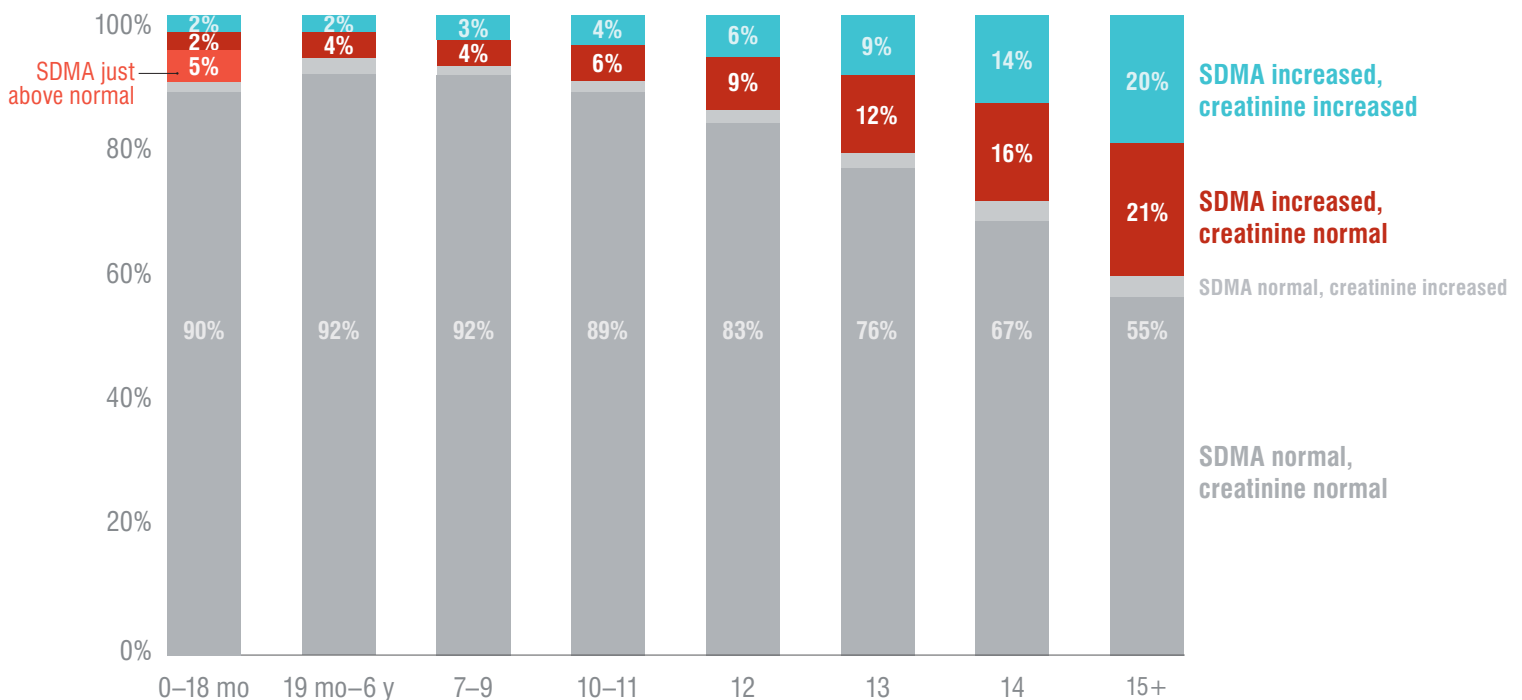


Figure 3. Prevalence of kidney disease increases with age in dogs (n = 537,814).



A closer look at SDMA results

Current understanding of results when SDMA is increased and creatinine is normal

SDMA is a more sensitive indicator of kidney function in animals. SDMA has been shown to increase earlier than creatinine in dogs and cats with CKD,^{1,2,3} and unlike creatinine, SDMA is not impacted by lean muscle mass.^{9,10} Therefore, it is not surprising that especially in thin, older animals with CKD their creatinine can be normal; without SDMA, their kidney disease would be overlooked. For an animal with increased SDMA and normal creatinine concentrations, the most common cause would be that the dog or cat has early CKD. However, CKD by definition is an irreversible disease. An increased SDMA with a normal creatinine may also be seen in animals with reversible kidney damage if the underlying cause is identified and treated or resolves on its own. Examples would include pyelonephritis and acute kidney injury secondary to infections (e.g., leptospirosis) or drug therapy (e.g., nonsteroidal anti-inflammatory drugs).

Current understanding of results when creatinine is increased and SDMA is normal

Questions arise about the accuracy of SDMA in cases where creatinine is increased and SDMA is normal. This is understandable given that SDMA has been shown to be a more sensitive biomarker of kidney function. The overall incidence of this combination of results is extremely low, seen in only 1% of feline samples and 2% of canine samples submitted. This is an area of active investigation. Our current understanding for causes of these results, supported by statistical analysis, is:

Assay and biologic variability: The most common cause is either SDMA and/or creatinine is at or very near the upper limit of the reference interval. While SDMA usually increases earlier than creatinine, there is biologic and assay variability that could contribute to these rare results where creatinine is increased and SDMA is normal. SDMA and creatinine results will likely align with repeat testing over time.

Breed impact: Creatinine reference intervals are established on a population basis. Greyhounds and Great Pyrenees are the two breeds whose creatinine concentrations are higher than other breeds and often fall above the reference interval while their SDMA concentrations remain normal. Additional studies evaluating SDMA in greyhounds are underway.

Muscle impact: Creatinine is impacted by lean muscle mass, whereas SDMA is not. In highly muscled dogs, their creatinine concentrations may fall above the reference interval while their SDMA concentrations remain normal.

Sample quality: Severe hemolysis may artifactually lower SDMA concentrations. Repeat testing on a clear nonhemolyzed sample is recommended for a more accurate measurement of SDMA concentration.

SDMA in puppies and kittens

On a population basis, median SDMA results appear to be slightly higher (approximately 1 $\mu\text{g/dL}$) in puppies and kittens. In figures 2 and 3, 90% of puppies and 86% of kittens have SDMA results within the reference interval. Of the 9% of puppies and 14% of kittens that have an increased SDMA, 5% and 6% respectively have SDMA concentrations just above the reference interval (15 or 16 $\mu\text{g/dL}$). SDMA results in puppies and kittens with these slight increases should be interpreted in light of other findings and monitored over time to see if they normalize or increase. The cause of this slight increase is unknown at this time, but physiological roles for protein arginine methylation include signal transduction, mRNA splicing, transcriptional control, DNA repair, and protein translocation. It is postulated that in growing animals, there is an increase in these processes, resulting in increased SDMA generation when the methylated proteins are degraded.

SDMA results in prerenal and postrenal azotemia

SDMA is a biomarker of kidney function and has been shown to correlate well to glomerular filtration rate (GFR). Therefore, it would be expected that SDMA would be increased secondary to a drop in GFR in animals with prerenal and postrenal azotemia. Studies are ongoing to determine if the impact of these conditions is any different on SDMA versus creatinine.

Summary

By using SDMA, veterinarians are better able to proactively assess the presence of kidney disease in over 2 times the number of cats and dogs than with traditional methods. SDMA typically increases earlier than creatinine and has been recognized by IRIS and other veterinary nephrologists as another tool to detect animals with early CKD. Early diagnosis of CKD provides the opportunity for earlier intervention and more effective kidney disease management. This in turn can improve the quality of pets' lives and help to delay the progression of the disease, possibly adding months or even years to the lives of pets with CKD.

Appendix

Canine

| Age | N:N | N:A | A:N | A:A | N | SDMA [†] 15 or 16 | SDMA [†] ≥17 |
|--------------|------------|-----------|-----------|-----------|----------------|-------------------------------|--------------------------|
| 0–18 mo | 91% | 1% | 7% | 2% | 31,314 | 5% | 2% |
| 19 mo–6 y | 92% | 2% | 4% | 2% | 136,669 | | |
| 7–9 | 92% | 2% | 4% | 3% | 151,966 | | |
| 10–11 | 89% | 2% | 6% | 4% | 105,492 | | |
| 12 | 83% | 2% | 9% | 6% | 42,948 | | |
| 13 | 76% | 3% | 12% | 9% | 31,895 | | |
| 14 | 67% | 3% | 16% | 14% | 20,497 | | |
| 15+ | 55% | 3% | 21% | 20% | 17,033 | | |
| Total | 87% | 2% | 6% | 4% | 537,814 | | |

Feline

| Age | N:N | N:A | A:N | A:A | N | SDMA [†] 15 or 16 | SDMA [†] ≥17 |
|--------------|------------|-----------|------------|------------|----------------|-------------------------------|--------------------------|
| <1 y | 86% | 0% | 12% | 2% | 7,874 | 6% | 6% |
| 1–5 y | 90% | 1% | 6% | 3% | 26,988 | | |
| 6–9 | 86% | 1% | 8% | 5% | 49,577 | | |
| 10–11 | 82% | 1% | 11% | 6% | 39,255 | | |
| 12–13 | 76% | 1% | 15% | 8% | 44,696 | | |
| 14 | 65% | 2% | 21% | 12% | 23,022 | | |
| 15 | 56% | 2% | 25% | 17% | 21,587 | | |
| 16 | 46% | 2% | 30% | 22% | 15,411 | | |
| 17 | 40% | 3% | 32% | 26% | 10,618 | | |
| 18+ | 31% | 3% | 33% | 33% | 11,301 | | |
| Total | 73% | 1% | 16% | 10% | 250,329 | | |

N:N SDMA and creatinine within reference interval

N:A SDMA within and creatinine exceeds reference interval

A:N SDMA exceeds and creatinine within reference interval

A:A SDMA and creatinine exceed reference interval

SDMA reference interval for dogs and cats: 0–14 µg/dL

Creatinine reference interval for dogs: 0.5–1.5 mg/dL

Creatinine reference interval for cats: 0.9–2.5 mg/dL

Notes

*Of the chemistry panels submitted between July and October 2015; n = 250,329 for the cat and n = 537,814 for the dog.

†The large majority of these increased creatinine samples in the cat and the dog also had an SDMA concentration above the reference interval; creatinine increased and SDMA normal results were seen in only 1% of feline samples and 2% of canine samples submitted. See section entitled "Current understanding of results when creatinine is increased and SDMA is normal" for discussion on these cases.

‡SDMA is measured in µg/dL.

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