AKI to CKD and everything in between: getting to grips with confusing renal diagnostics

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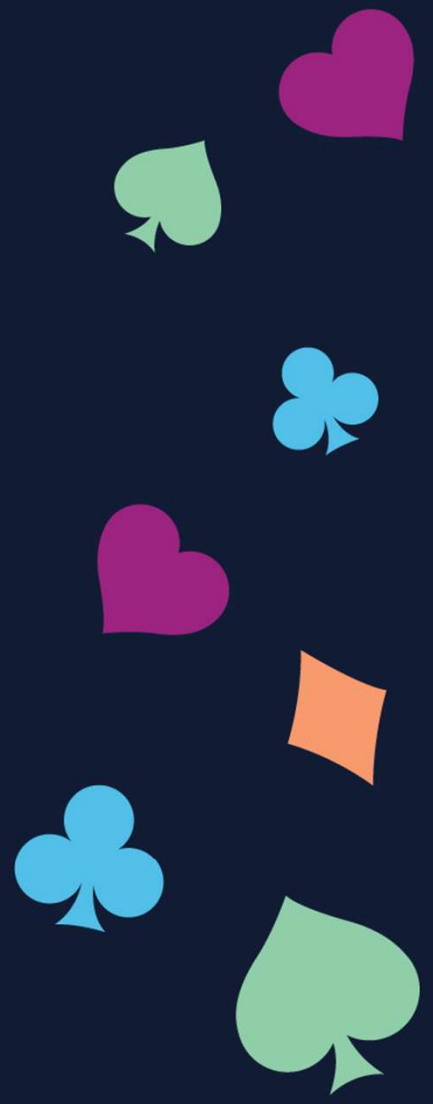
Financial Disclosure

I am a full-time IDEXX; The relationship does not influence the medicine. It *may* influence a few of my images…



The information contained herein is intended to provide general guidance only. Diagnosis, treatment, and monitoring should be patient specific and is the responsibility of the veterinarian providing primary care.

Learning objectives

By the end of this presentation, participants should be able to:

1. Compare and contrast the significance of kidney injury vs. chronic kidney disease
2. Identify biomarkers of acute and active kidney injury, including urinary cystatin B
3. Understand the cellular sources for cystatin B and the significance of elevated urinary concentrations
4. Apply acute injury concepts to clinical cases

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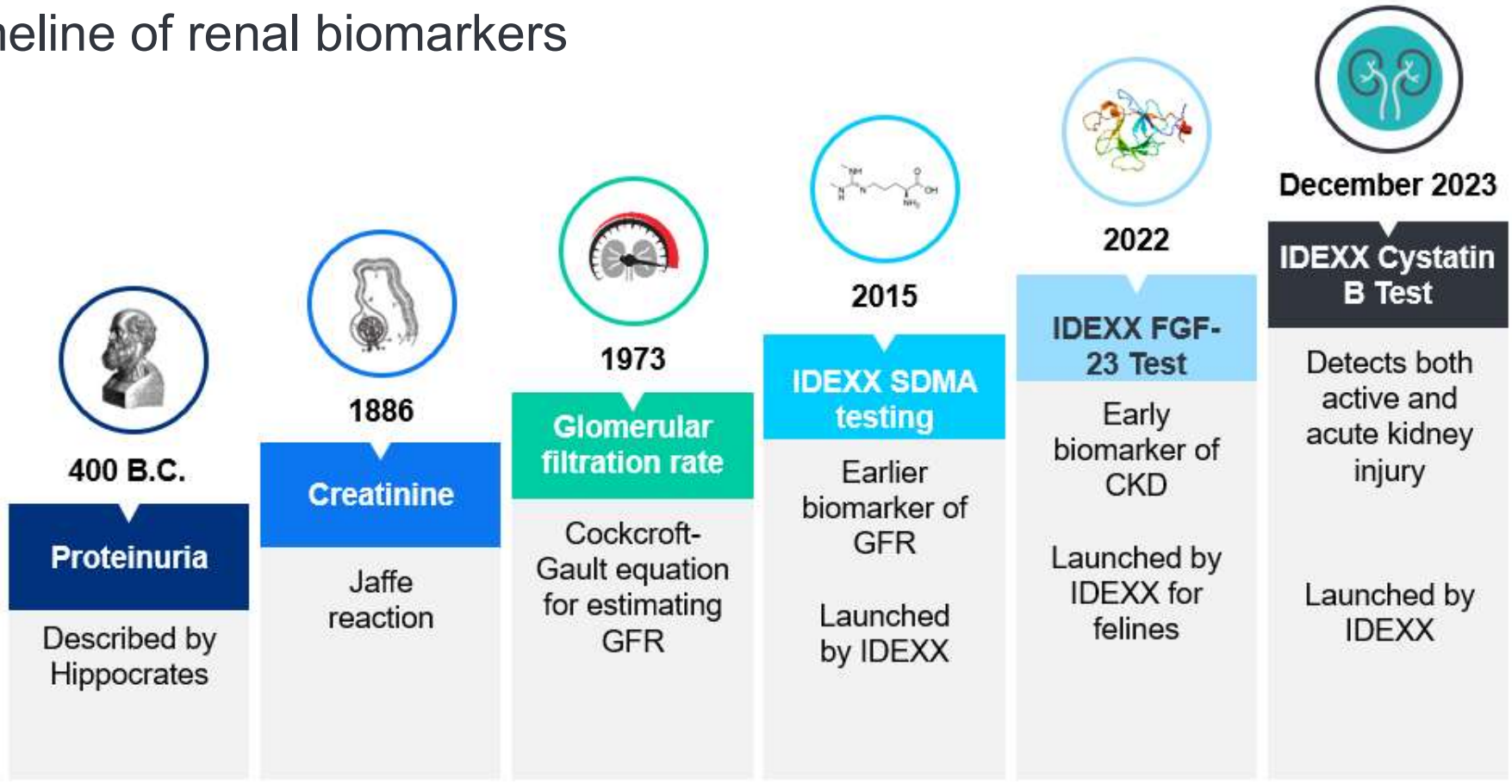
Timeline of renal biomarkers



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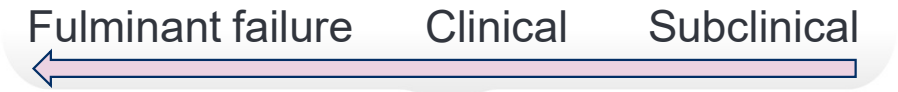
Terminology can be confusing; ARF, AKI, ATI, ATN



Acute Renal Failure

- Failure has specific definition of >90% loss of function with clinical effects
- Was a term often used to characterize significant loss of kidney function
  - Retention of uremic toxins
  - Dysregulation of fluid
  - Electrolyte and acid-base imbalance

Acute Kidney Injury

- Acute → short time span, generally ≤ 24-48 hours
- Impact disrupts renal cellular structure and function
- Injury does not necessarily = failure, or even azotemia
- Damage can be reversible

Acute tubular injury (ATI) or necrosis (ATN) is the most common cause of AKI in dogs and cats

Active Kidney Injury

- Often cannot characterize the timeline
- Inciting cause and time of onset are not always known
- Diagnostics indicate ongoing and sustained injury
- Distinguish **active kidney injury** from **kidney dysfunction**

J. Himmelfarb, T.A. Ikizler, Acute kidney injury: changing lexicography, definitions, and epidemiology, Kidney International,Volume 71, Issue 10,2007,Pages 971-976,ISSN 0085-2538, https://doi.org/10.1038/sj.ki.5002224.
Kellum, John A., Claudio Ronco, and Rinaldo Bellomo. "Conceptual advances and evolving terminology in acute kidney disease." Nature Reviews Nephrology 17.7 (2021): 493-502.

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Acute kidney injury (AKI) vs. chronic kidney disease (CKD): Why do we care?

AKI

- Early detection to prevent progression
- Institute supportive care and specific therapy when possible
- Determine resolution or progression
- Short-term financial and emotional investments are intense
- Prolonged hospitalization: associated with higher morbidity and mortality

CKD

- Early detection/intervention in attempt to slow progression
- Institute dietary therapy, supportive care
- Determine likelihood of rapid progression
- Long-term financial, emotional, and time commitments
- Usually outpatient therapy; when hospitalization is required, usually associated with low morbidity and mortality

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Hallmarks of AKI (vs. CKD)

History and physical exam

+ Acute onset—hours to days
+ Toxin exposure (lily, grapes, NSAIDs, anesthetics…)
+ Renomegaly, renal pain
+ Lack of other PE change
+ Bradycardia (if severe hyperkalemia)
+ Hypothermia

Lab findings

+ Hyperkalemia
+ Urinary granular casts, normoglycemic glucosuria

Imaging

+ Renomegaly in 70%
+ Hydroureter, pyelectasia, hydronephrosis
+ Ureteral calculi
+ Normal parathyroid gland

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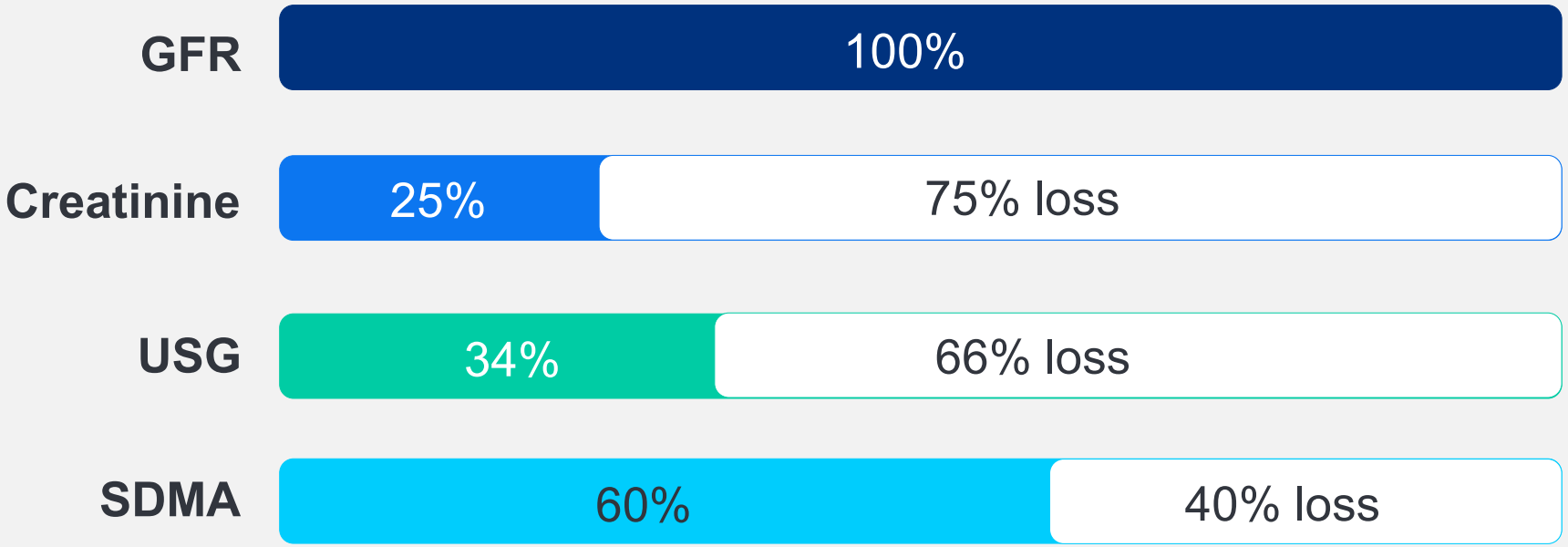
Performance of current renal “functional” biomarkers (estimates of GFR)



Source: Hall JA, Yerramilli M, Obare E, Yerramilli M, Almes K, Jewell DE. Serum concentrations of symmetric dimethylarginine and creatinine in dogs with naturally occurring chronic kidney disease. *J Vet Intern Med*. 2016;30(3):794–802. doi:10.1111/jvim.13942

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GFR biomarkers fall short as early detectors of kidney disease

Categorization of biomarkers and analytes used to evaluate kidney function and injury

Indirect markers of function	Urine-based markers	Other important analytes	Acute kidney injury markers
Most specific (limited extrarenal influences): + SDMA + Creatinine **Less specific (more extrarenal influences):** + BUN + Phosphorus	**Urinalysis** + Physical + Chemical + Sediment **UPC**	+ Potassium + Sodium/chloride + Calcium + Albumin/TP + Hematocrit + FGF-23	+ Cystatin B + Urine Clusterin + NGAL

You need broad assessment to understand kidney health

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What can we measure in clinical practice?

Glomerular function

How well are the kidneys clearing waste from the body (GFR)

Creatinine, SDMA, BUN

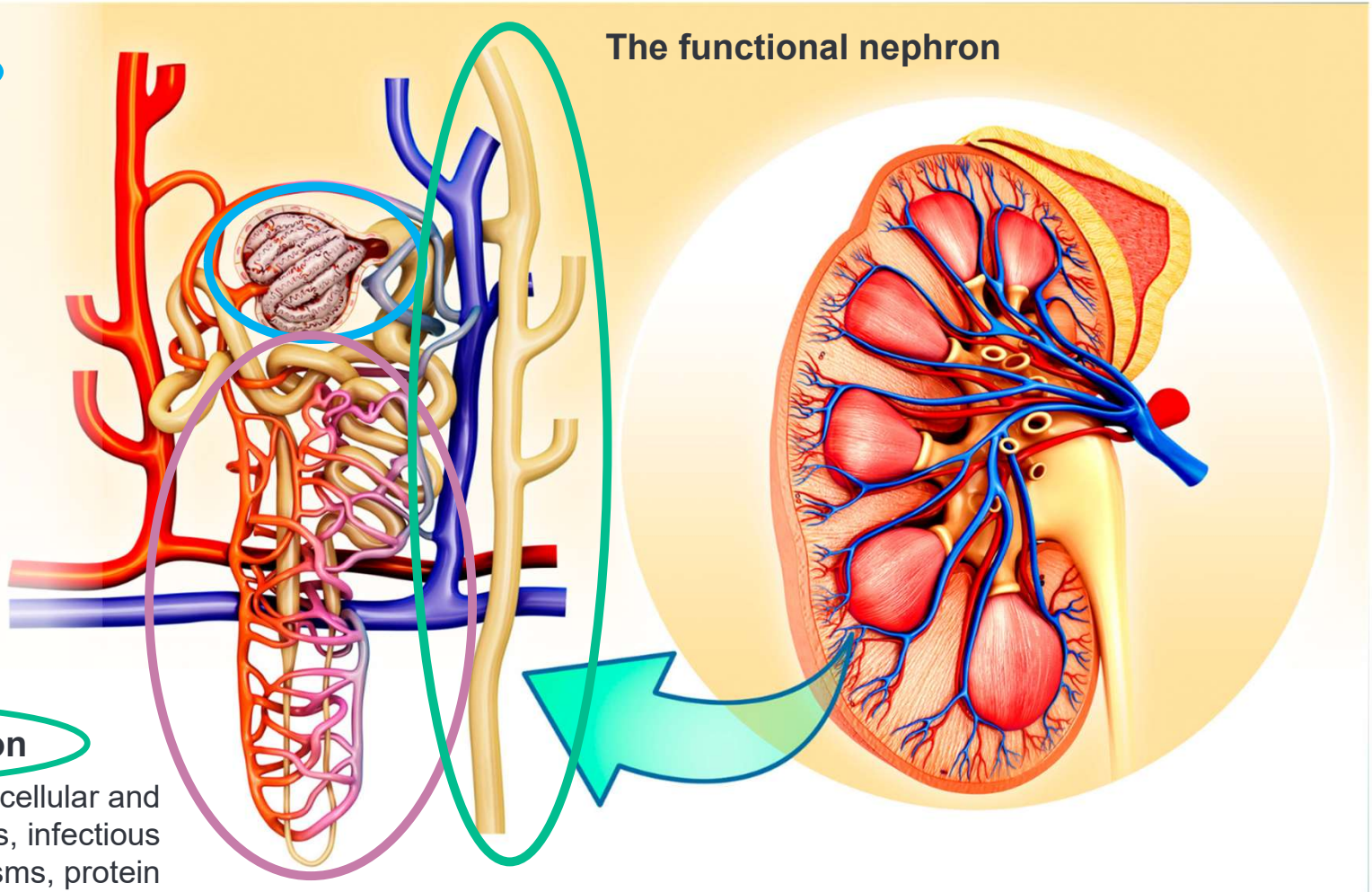
Tubular function

Important in solute and water management

Urine concentration and protein; serum and urine electrolytes, glucose, acid-base

Urine composition

Concentration/volume, pH, cellular and crystalline elements, infectious organisms, protein



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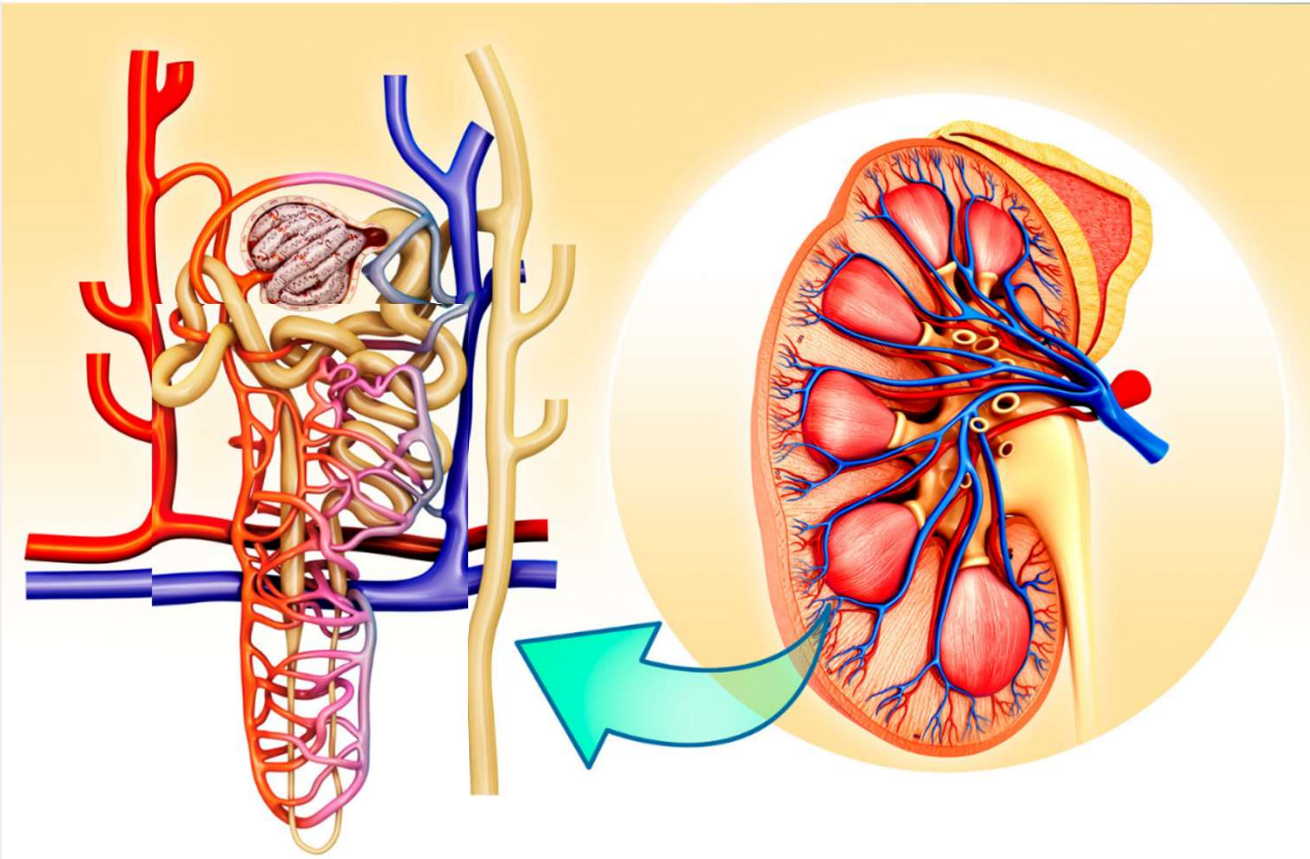
Renal tubules are where the action **really** is

Tubular function

- The actual work of the kidney primarily takes place here. Filtering, reabsorbing, and secreting solutes and water
- Impact urine concentration and what is excreted
- Dysfunction can impact electrolytes, protein levels, glucose, acid-base balance
- Captured in chemistry panel and urinalysis



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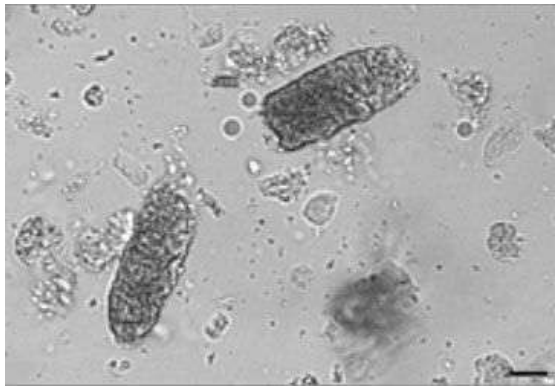
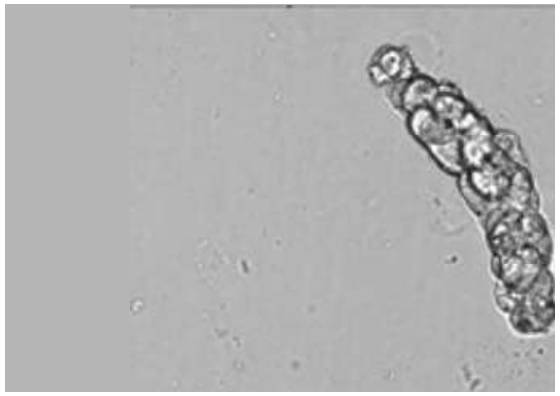
Traditional renal **injury** markers are good, not great

+ Proteinuria
+ Hematuria, pyuria
+ Bacteriuria
+ Renal epithelial cells in the urine
+ Glucosuria (normoglycemia)
+ Cylindruria (casts)
+ Decreased USG

Granular casts





Cellular cast

Source: IDEXX SediVue Dx® images

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Functional markers are in blood

Tubular injury markers are in the urine

Take-home message:

You can’t assess kidney health without urine

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Veterinary criteria – IRIS AKI grading

Table 1: IRIS AKI Grading Criteria

AKI Grade	Blood Creatinine	Clinical Description
Grade I	<1.6 mg/dl (<140 µmol/l)	Nonazotemic AKI: a. Documented AKI: (historical, clinical, laboratory, or imaging evidence of AKI, clinical oliguria/anuria, volume responsiveness‡) and/or b. Progressive nonazotemic increase in blood creatinine: ≥ 0.3 mg/dl (≥ 26.4 µmol/l) within 48 h c. Measured oliguria (<1 ml/kg/h)# or anuria over 6 h
Grade II	1.7 – 2.5 mg/dl (141 – 220 µmol/l)	Mild AKI: a. Documented AKI and static or progressive azotemia b. Progressive azotemic: increase in blood creatinine; ≥ 0.3 mg/dl ≥ 26.4 µmol/l) within 48 h),or volume responsiveness‡ c. Measured oliguria (<1 ml/kg/h)# or anuria over 6 h
Grade III	2.6 – 5.0 mg/dl (221 – 439µmol/l)	
Grade IV	5.1 – 10.0 mg/dl (440 – 880 µmol/l)	Moderate to Severe AKI: a. Documented AKI and increasing severities of azotemia and functional renal failure
Grade V	>10.0 mg/dl (>880 µmol/l)	

(‡Volume responsive is an increase in urine production to >1 ml/kg/h over 6 h; and/or decrease in serum creatinine to baseline over 48 h)

Risk
Nonazotemic

Injury
Mildly azotemic

Failure
Moderately to severely azotemic

IRIS International Renal Interest Society

http://www.iris-kidney.com/education/index.html

Subgrade

Each grade of AKI is further subgraded as:
1. Non oliguric (NO) or oligo-anuric (O)
2. Requiring renal replacement therapy (RRT)

http://www.iris-kidney.com/guidelines/grading.html

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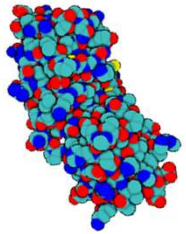
Can we do any better?

YES!!! We can!

Cystatin B bridges the gap in our abilities to detect early and active renal injury

What is cystatin B?



- Member of cystatin family
  - Protease inhibitors that help protect against leakage of proteolytic enzymes from lysosomes
  - Trace amounts in the serum of healthy subjects
- A small, intracellular protein
  - 11 kDa (11,000 daltons)
  - Ubiquitous in many cells, including proximal renal tubular cells
- Freely filtered at the glomerulus
- Increased urinary [cystatin B] indicates active, ongoing tubular injury
  - Think of it as the ALT of the kidney

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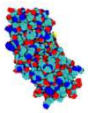
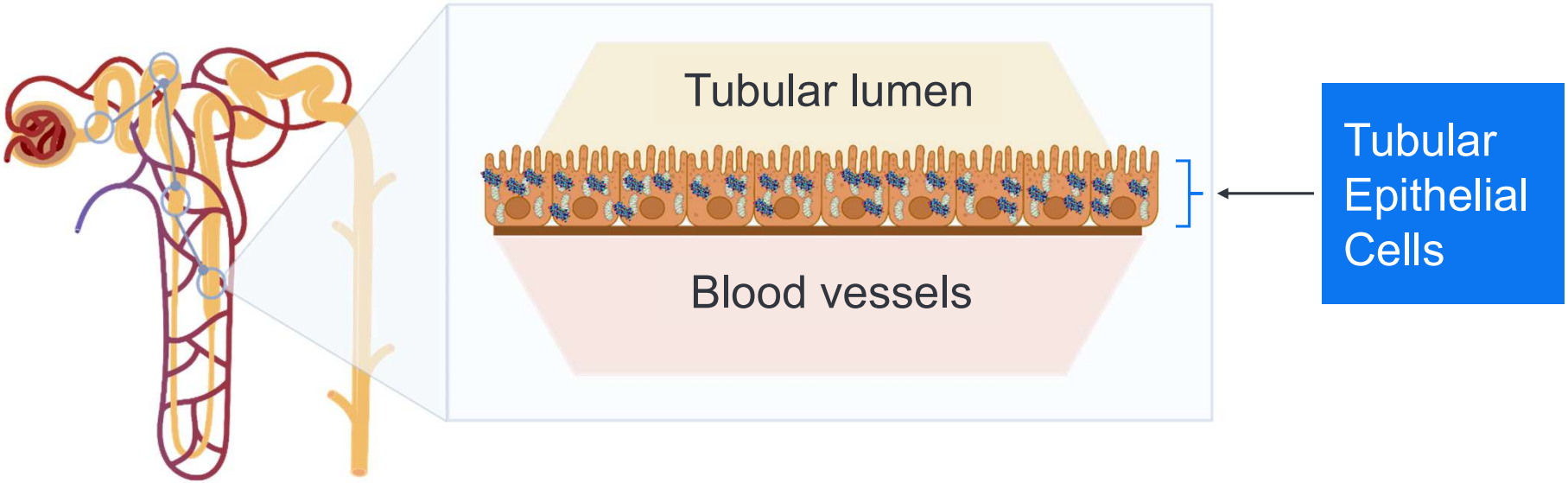
Cystatin B is a very small protein contained in epithelial cells of the renal tubules





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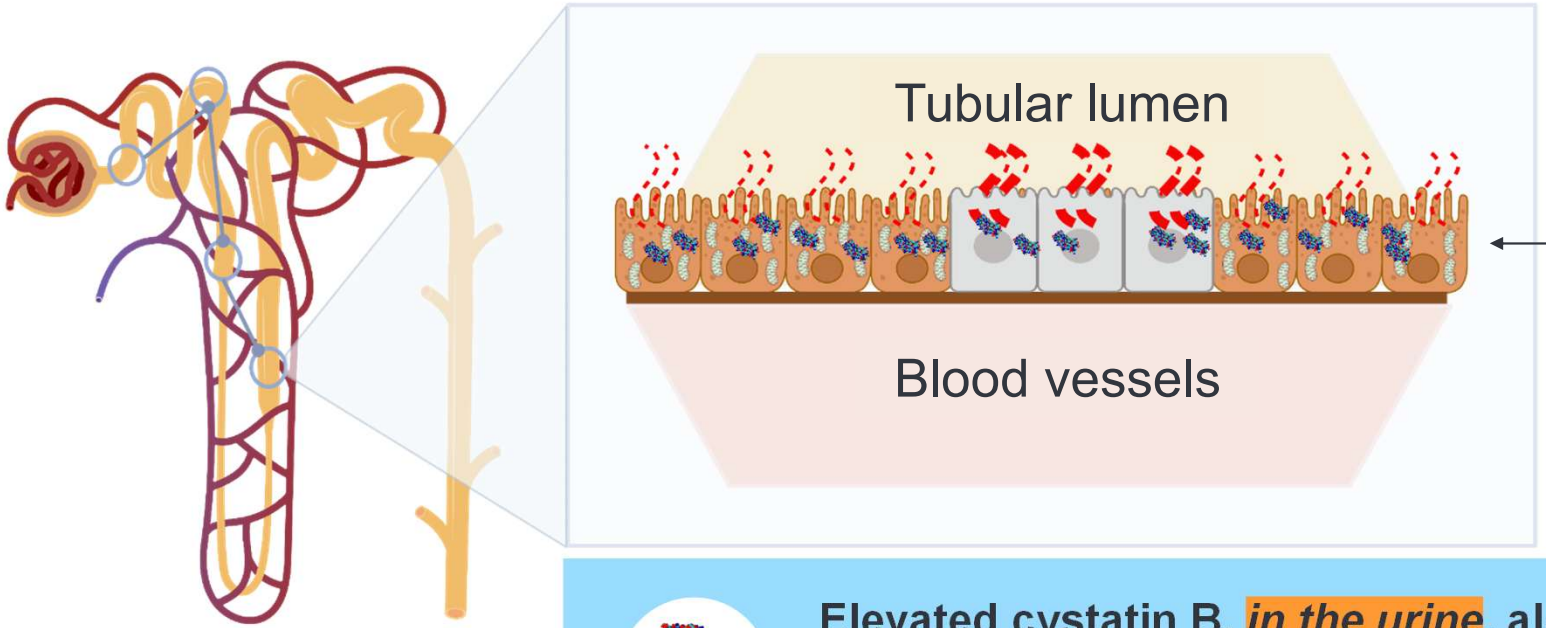
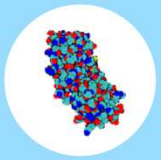
During **active or acute kidney injury**, renal tubular epithelial cells can be damaged



Cystatin B leakage from injured or necrosed tubular epithelial cells



Elevated cystatin B, *in the urine*, alerts to earlier, ongoing, and unresolved kidney injury, and can occur with or without increases in functional markers,

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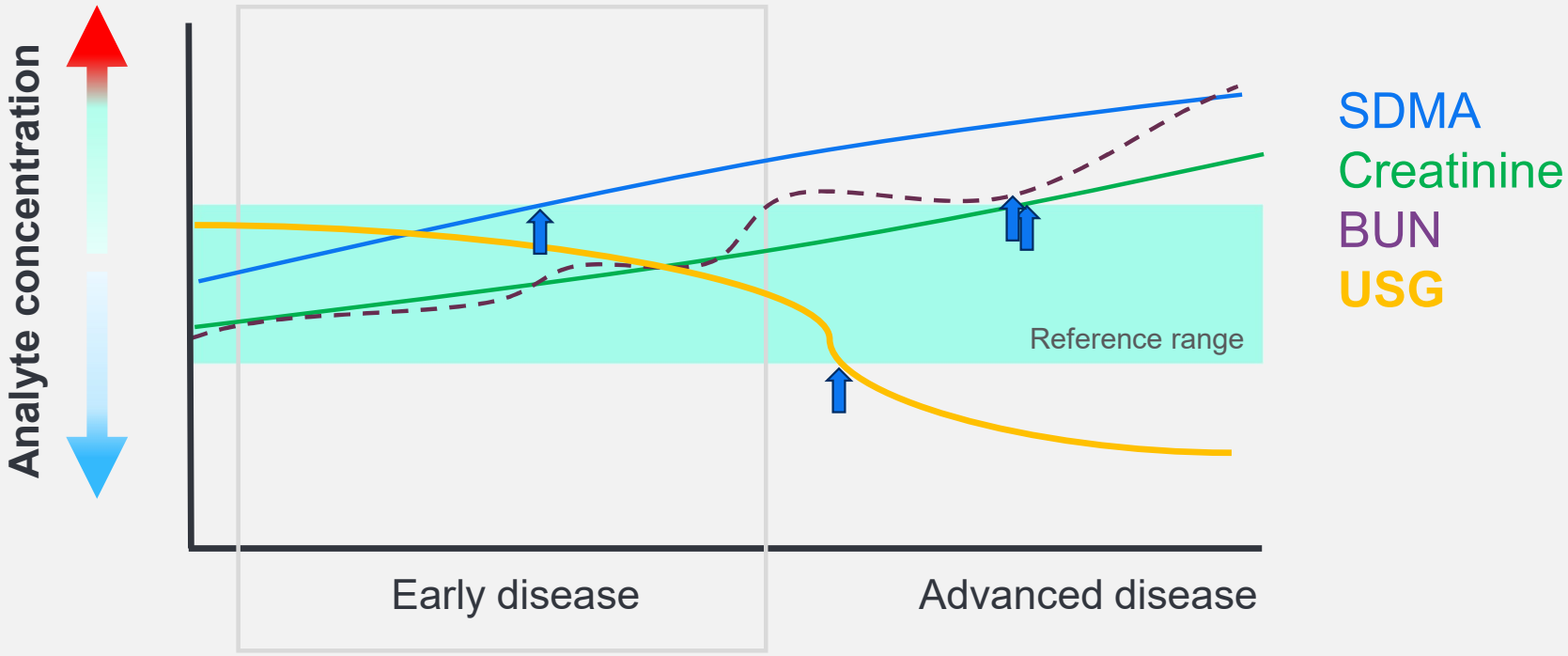
Kidney injury markers are additive to current indirect functional markers



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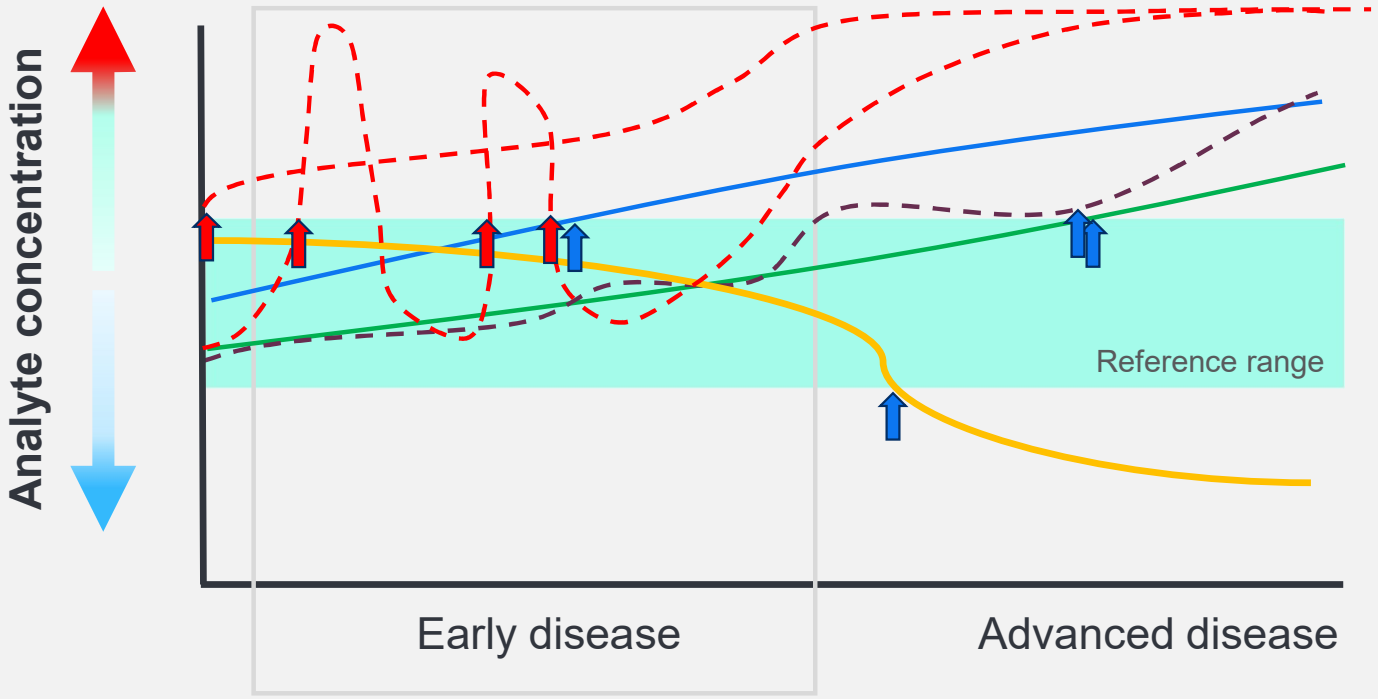
Kidney injury markers are additive to current indirect functional markers



Renal tubular markers
SDMA
Creatinine
BUN
USG

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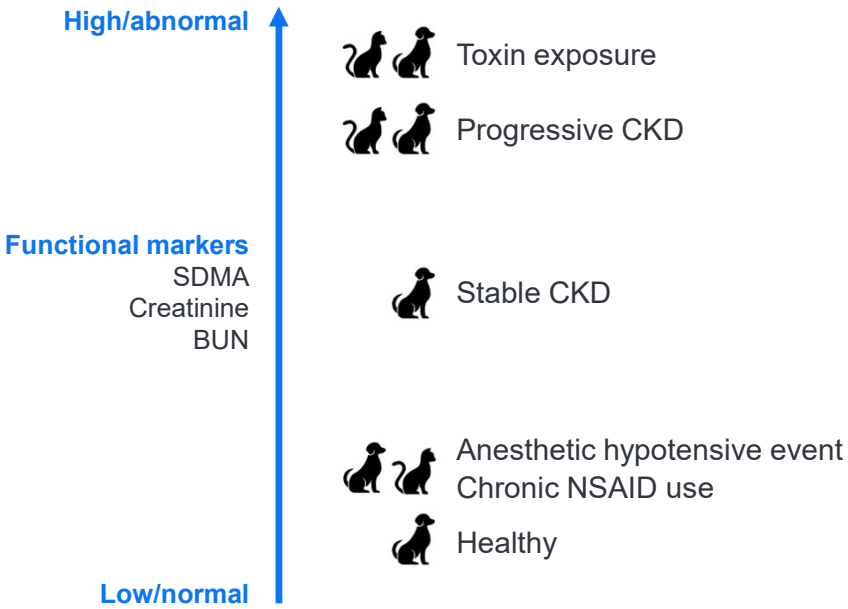
Traditional diagnostics only allow for case evaluation by functional markers



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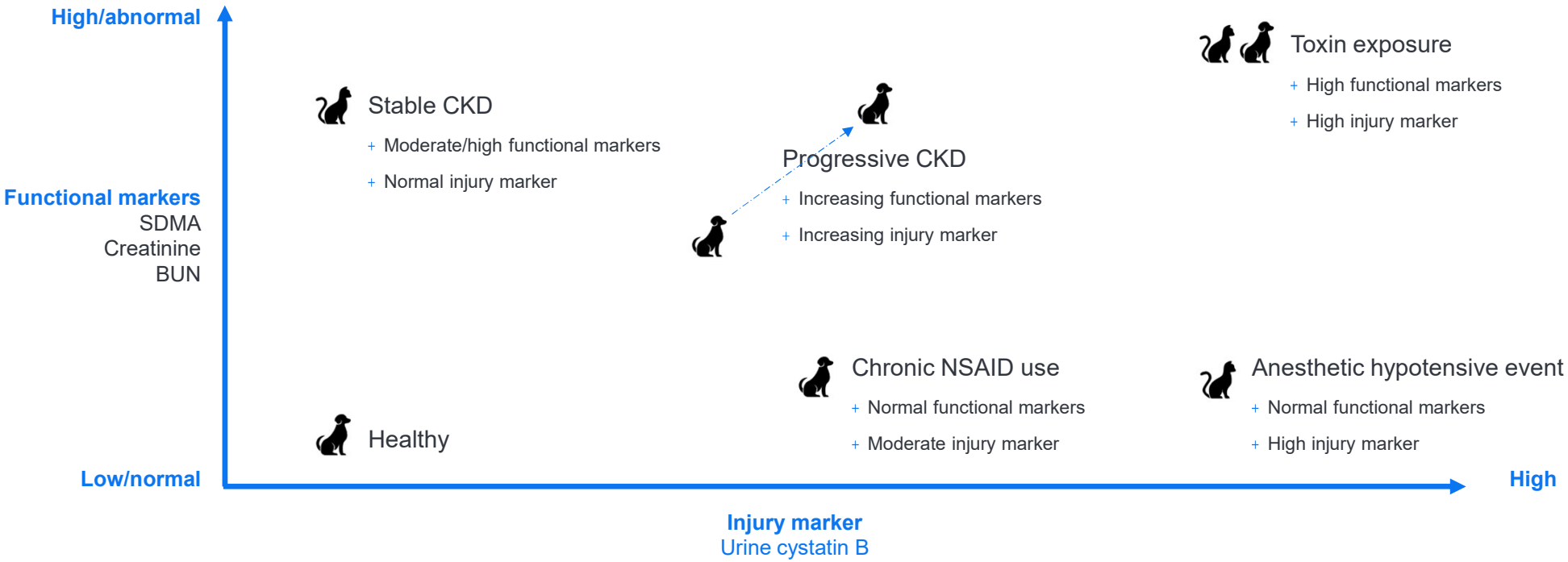
Addition of an injury marker provides better case discrimination and management



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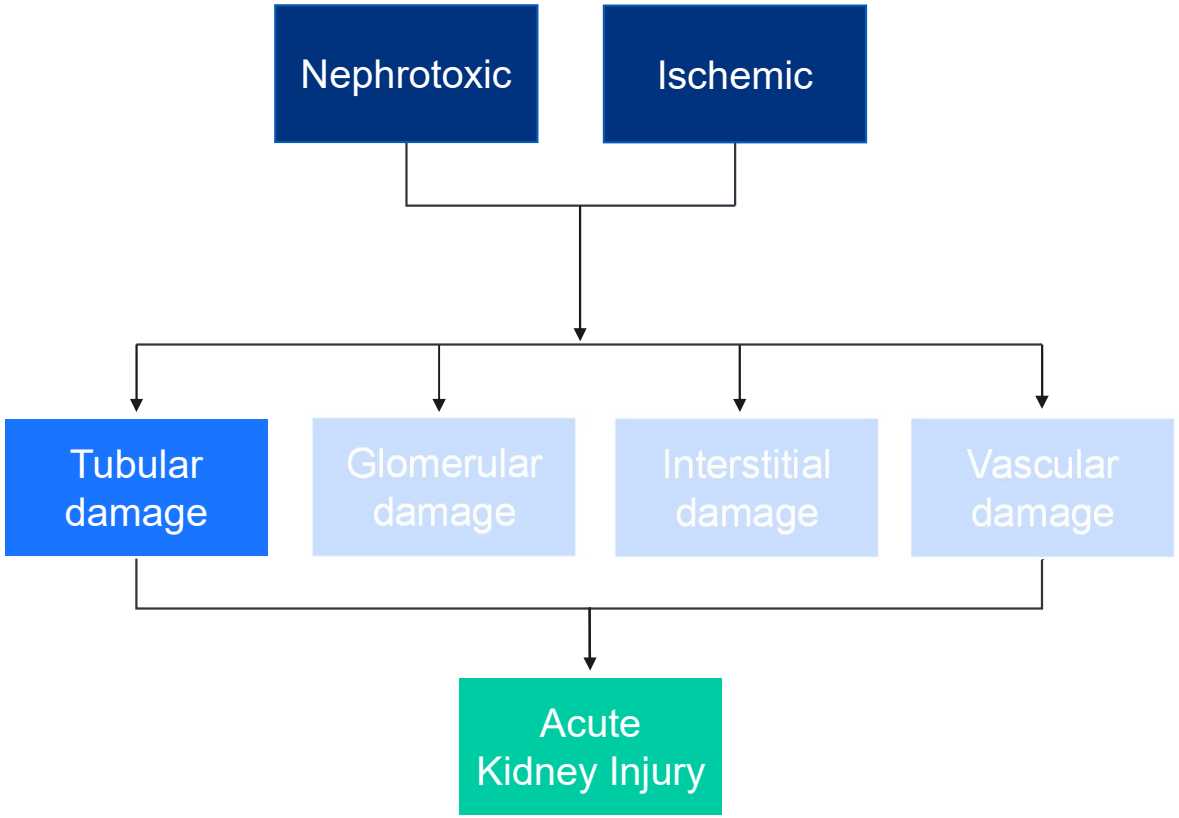
Pathophysiology of AKI



Common etiologies:

+ Infectious diseases
+ Nephrotoxins
+ Systemic diseases with secondary renal involvement (inflammation)
+ Alterations in hemodynamics
+ Obstructive disorders

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Causes of AKI include:

Cat

+ Toxins (plants, chemotherapeutics)
+ Pyelonephritis
+ Acute pancreatitis
+ Marked dehydration
+ Obstructive disorders
+ Etiology unknown ~30%

Dog

+ Toxins (plants, chemotherapeutics, foods)
+ Pyelonephritis
+ Acute pancreatitis
+ Marked dehydration
+ Obstructive disorders
+ Leptospirosis
+ Lyme nephritis
+ Congestive heart failure

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AKI can develop in hospitalized patients: Monitor and grade daily

+ Dehydration
+ Age > very young or old
+ Diuretic or nephrotoxic drug therapy
+ Hypokalemia or hypercalcemia
+ Sepsis
+ Congestive heart failure
+ Acute pancreatitis
+ Systemic hypertension
+ CKD

Avoid iatrogenic AKI!
Nephrotoxic drugs
Hemodynamic instability
Fluid overload

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Abnormal renal functional markers reflect progression of injury to dysfunction *after* the fact: Early recognition of renal injury is an opportunity to *change course of disease*

	Wellness labs				6 months later			
	SDMA	14	0 – 14 µg/dL		SDMA	11	0 – 14 µg/dL	
	SDMA	14	0 – 14 µg/dL		SDMA	23	0 – 14 µg/dL	

Stable functional renal markers

Progressive functional renal markers

Two dogs seen for general check up

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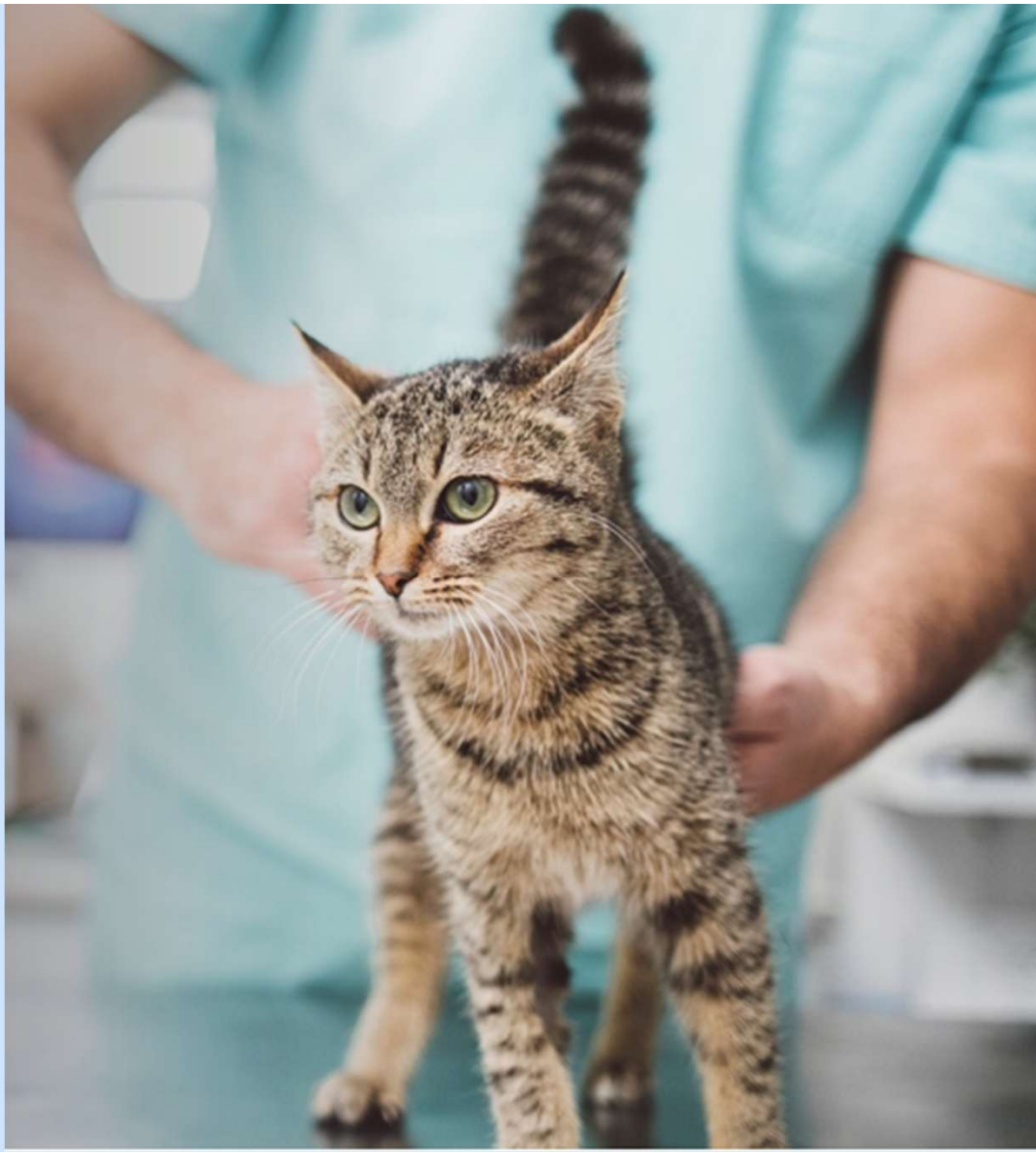
Initial treatment of AKI



Initial therapy for AKI; back to the basics

+ Address hydration and volemic status
+ Institute disease-specific therapy whenever possible
+ Address complications of AKI
+ Avoid and monitor for complications of therapy
+ Keep the patient comfortable
+ Prevent further renal injury
+ Address nutrition

Use serial evaluations of IRIS AKI grading for objective measure of response to therapy; adapt/adjust accordingly

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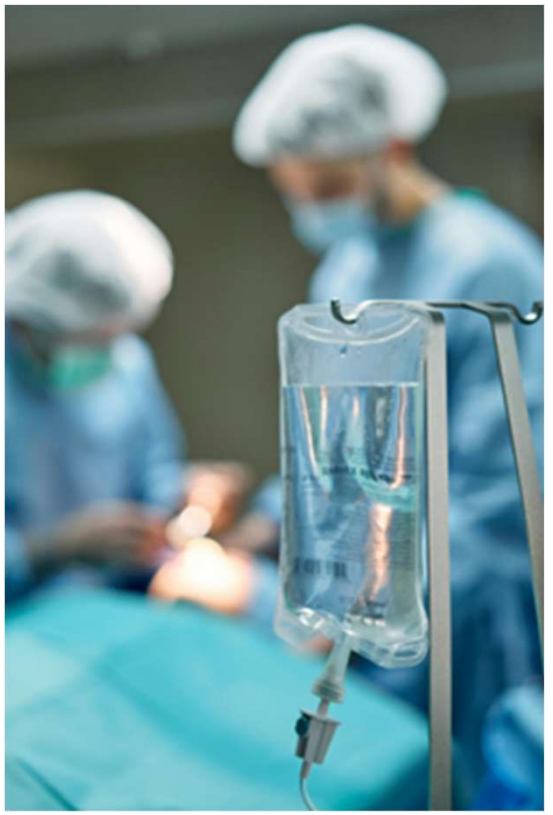
Fluid therapy for kidney disease: Less may be more

- Fluids are drugs—avoid overdose
- Fluids do not improve kidney function
- Hypervolemia causes AKI and kills patients that already have it
- Not every patient with kidney disease (acute or chronic) needs fluids!!!



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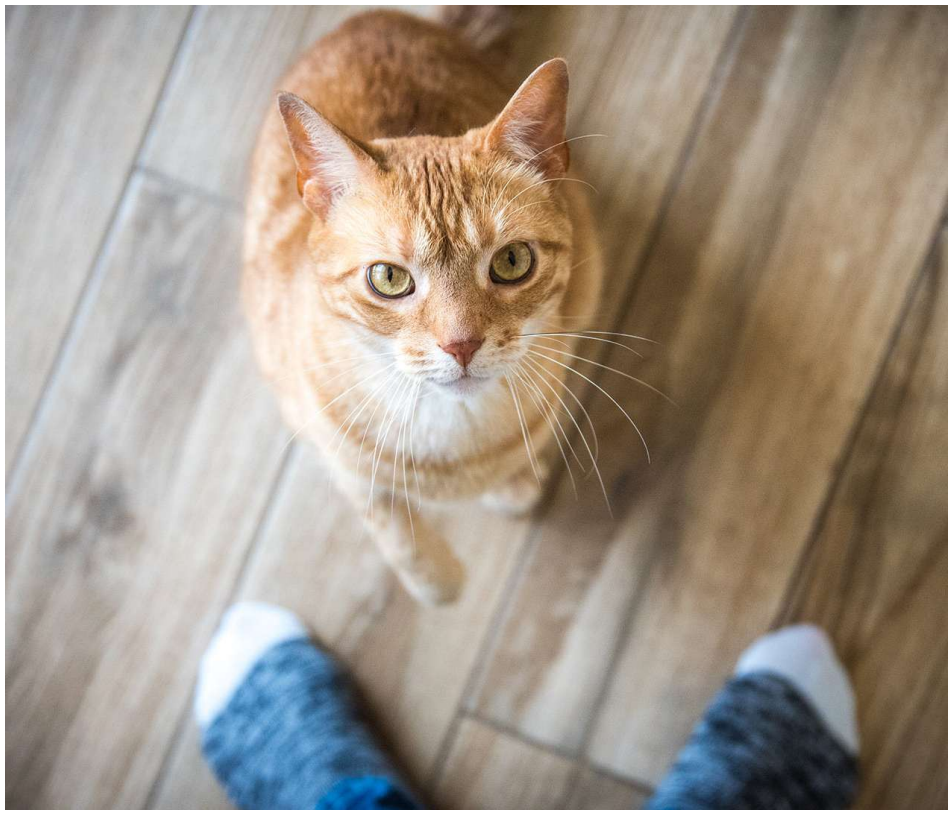
Assessment of response to fluid therapy is essential

- Perfusion parameters: HR, CRT, mucous membranes, pulses, lactate, base excess
- Body weight 2-4x/day: >5%–10% increase slow or stop fluids
- Lung auscultation: ≥ q12 hrs, more frequently if any changes in RR/RE



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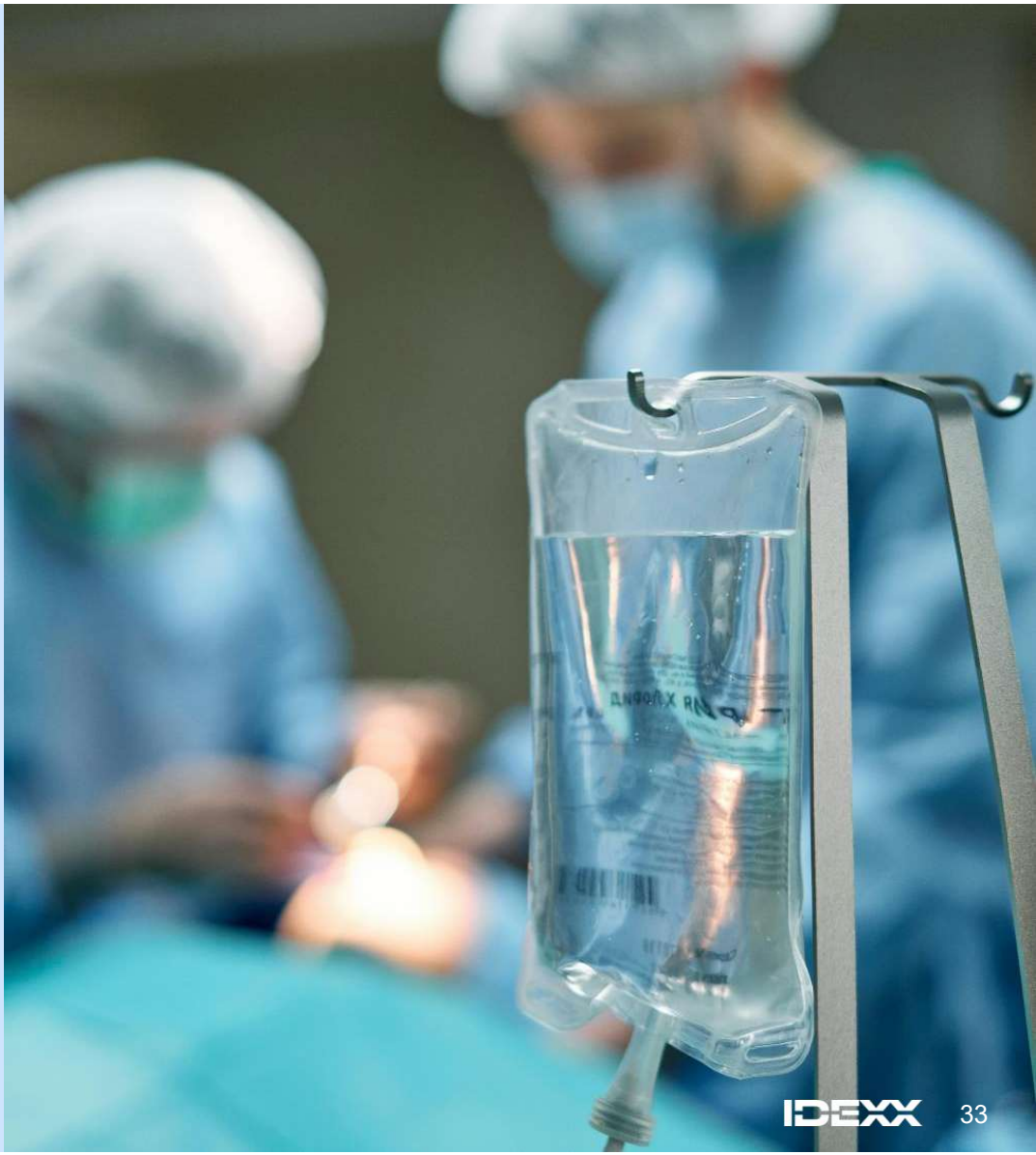
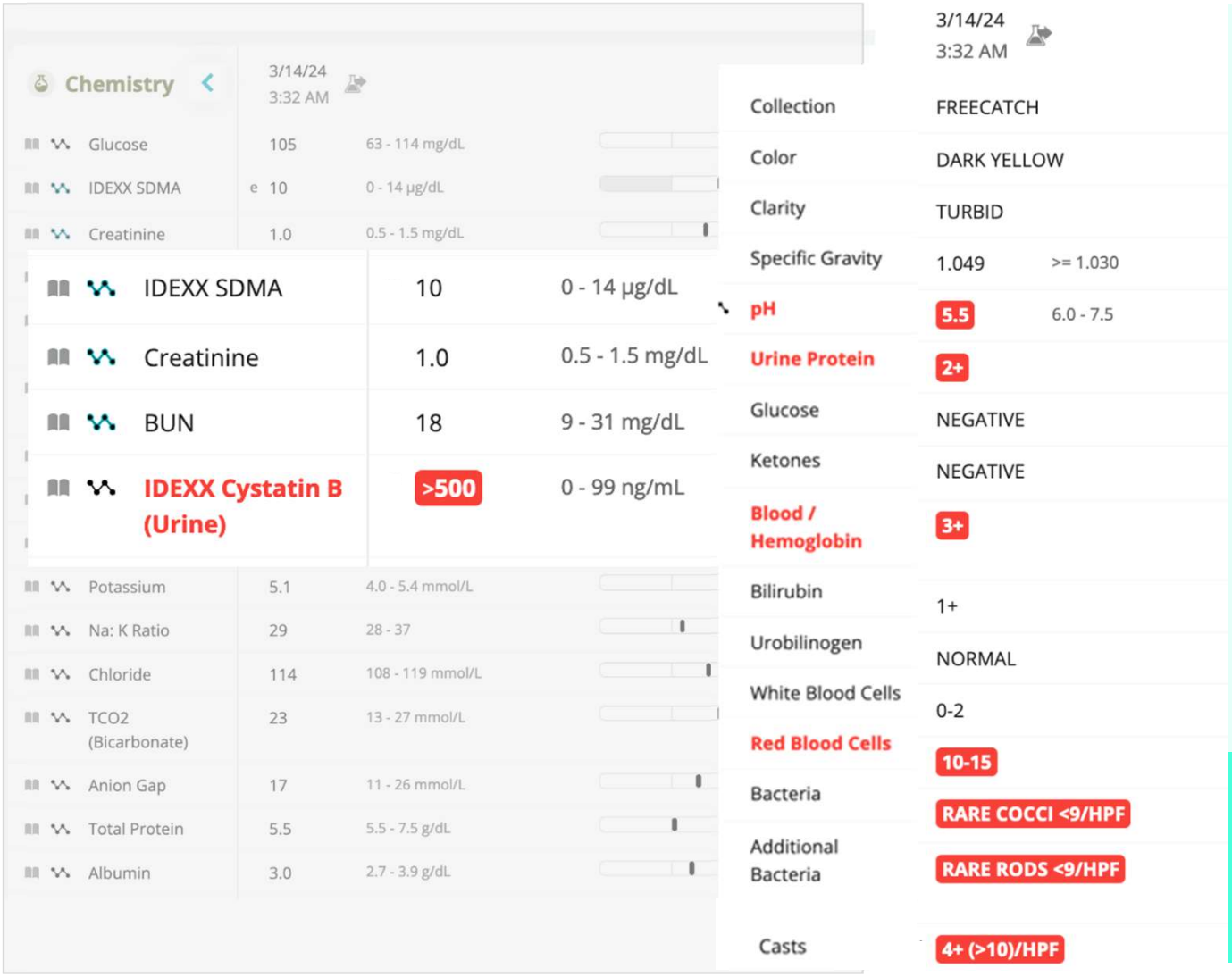
If azotemia worsens with IV fluid therapy, consider **decreasing** fluid rate.

Especially if total daily volume exceeds maintenance or if weight gain.



My dog ate some raisins.



Rover

+ 3-year-old MC MixB
+ Confirmed raisin ingestion
+ Amount/time prior to presentation uncertain
+ Previously healthy

Elevated urinary cystatin B, proteinuria, cylindruria

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Three days later, after IV fluids for 48 hours

Chemistry	3/17/24 1:07 AM	
IDEXX SDMA	8	0 - 14 µg/dL
Creatinine	1.2	0.5 - 1.5 mg/dL
BUN	26	9 - 31 mg/dL
IDEXX Cystatin B (Urine)	<50	0 - 99 ng/mL
Ratio		
Phosphorus	5.1	2.5 - 6.1 mg/dL
Calcium	9.5	8.4 - 11.8 mg/dL
Sodium	148	142 - 152 mmol/L
Potassium	5.1	4.0 - 5.4 mmol/L
Na: K Ratio	29	28 - 37
Chloride	114	108 - 119 mmol/L
TCO2 (Bicarbonate)	25	13 - 27 mmol/L
Anion Gap	14	11 - 26 mmol/L
Total Protein	**5.1**	5.5 - 7.5 g/dL
Albumin	2.7	2.7 - 3.9 g/dL
Globulin	2.4	2.4 - 4.0 g/dL

Urinalysis	3/17/24 1:07 AM
Collection	FREECATCH
Glucose	NEGATIVE
Ketones	a RACE
Blood / Hemoglobin	**3+**
Bilirubin	1+
Urobilinogen	NORMAL
White Blood Cells	0-2
Red Blood Cells	**30-50**
Bacteria	NONE SEEN
Additional Bacteria	
Epithelial Cells	1+ (1-2)/HPF
Mucus	NONE SEEN
Casts	NONE SEEN
Crystals	NONE SEEN

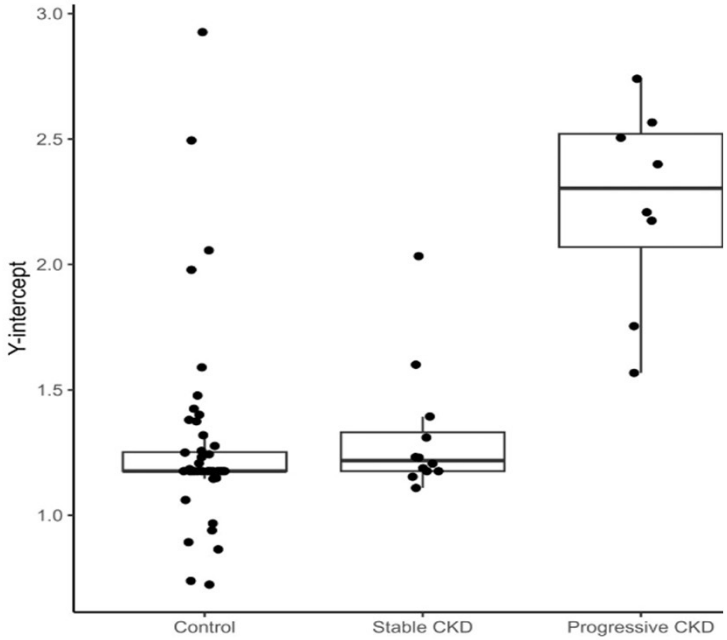
J Vet Diagn Invest 17:223–231 (2005)

Canine renal pathology associated with grape or raisin ingestion: 10 cases

All dogs had degeneration or necrosis (or both) of proximal renal tubules with basement membranes remaining intact, and epithelial regeneration was observed in 5 out of 10 cases.

Cystatin B has value with evaluating patients with CKD as well!

- CKD progressive and irreversible
- Rate of progression unpredictable
- Cystatin B identifies active, progressive injury in dogs with CKD
- Increased urinary cystatin B (uCysB) in dogs with IRIS Stage 1 CKD predicts rapid progression
- Identifies which dogs need more frequent monitoring



y-intercepts calculated from inverse urinary cystatin B (uCysB) vs. time

Segev, et al. J Vet Intern Med. 2023

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Uses for the IDEXX Cystatin B Test

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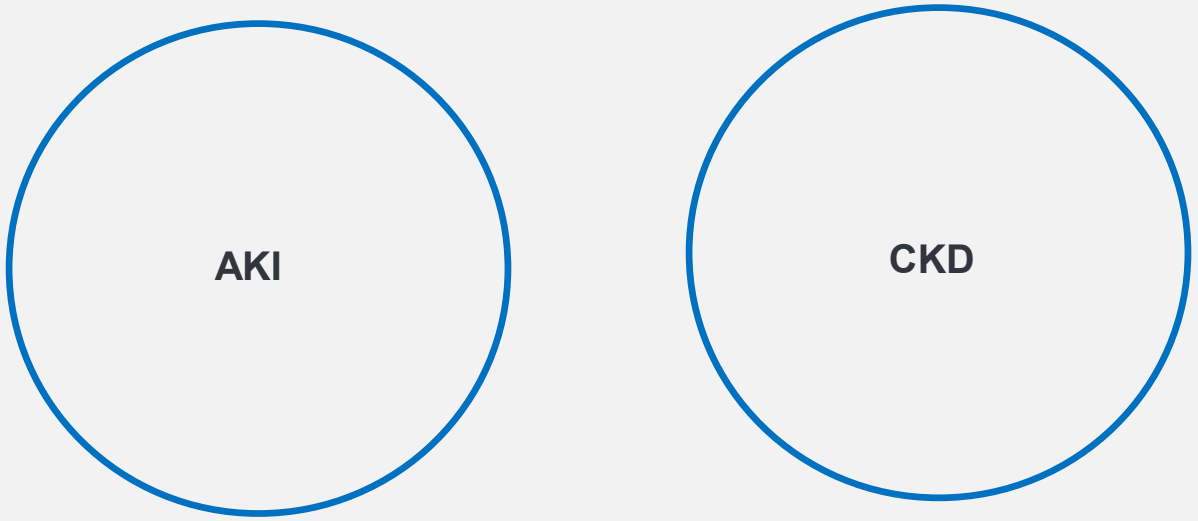
Back in the day…



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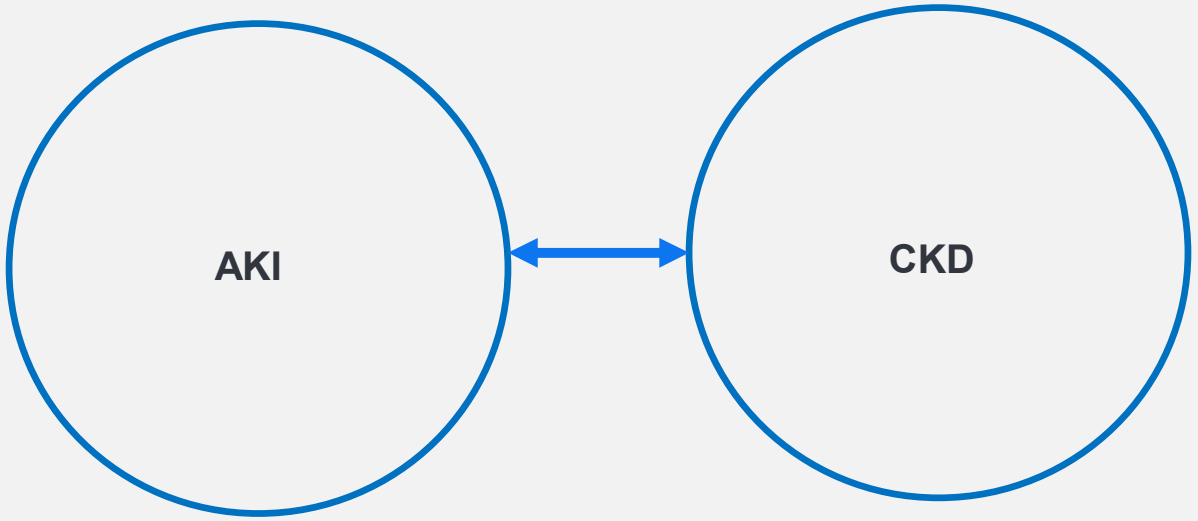
More contemporary view…

Your AKI patient may have or develop CKD



Your CKD patient may have concurrent active kidney injury

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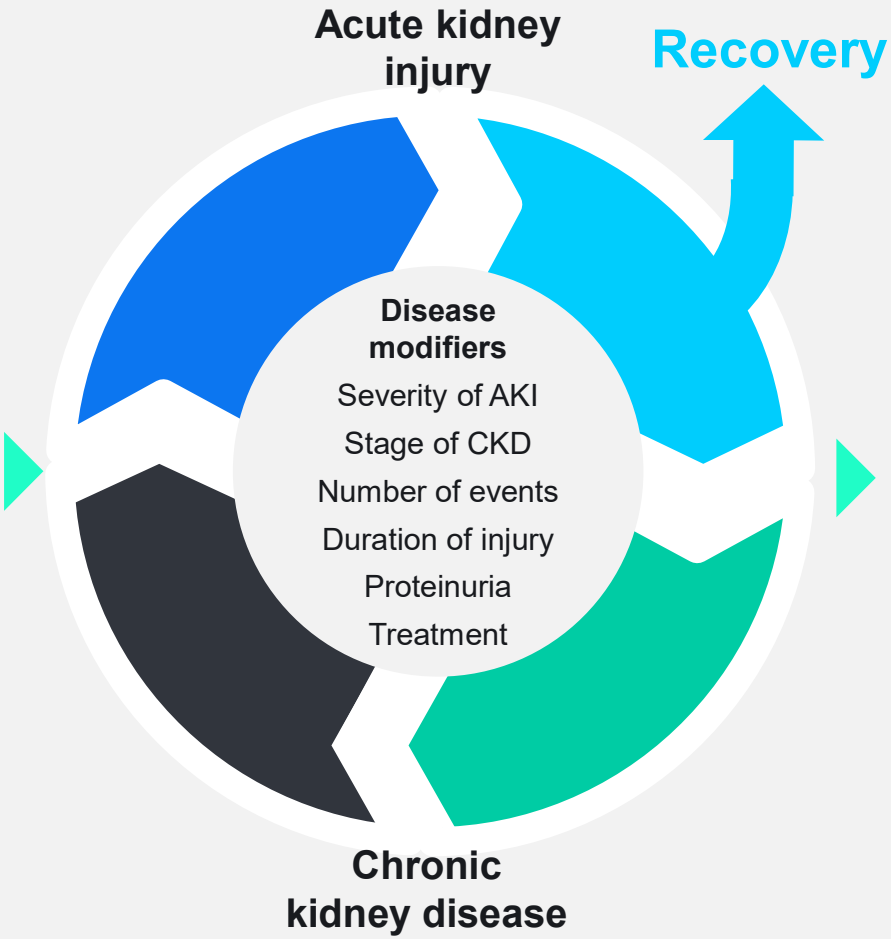
Kidney function in health and disease is impacted by risk factors, injury, and outcomes

Risk factors

- Breed
- Age
- Sex
- Diet
- Drugs
- Pre-existing disease
  - CKD
  - Hypertension
  - Metabolic disease
  - Cardiac disease



Outcomes

- Persistent damage
- Cardiovascular events
- Additional kidney events
- Diminished quality and quantity of life
- Cost events

Source: Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371(1):58–66. doi:10.1056/NEJMra1214243

IDEXX

STAGING CKD:

IRIS guidelines

		Stage 1 No azotemia (Normal creatinine)	Stage 2 Mild azotemia (Normal or mildly elevated creatinine	Stage 3 Moderate azotemia	Stage 4 Severe azotemia	
Creatinine in mg/dL						
Stage based on stable creatinine	Canine	Less than **1.4** (125 µmol/L)	**1.4–2.8** (125–250 µmol/L)	**2.9–5.0** (251–440 µmol/L)	Greater than **5.0** (440 µmol/L)	1
	Feline	Less than **1.6** (140 µmol/L)	**1.6–2.8** (140–250 µmol/L)	**2.9–5.0** (251–440 µmol/L)	Greater than **5.0** (440 µmol/L)	
SDMA in µg/dL						
Substage based on stable SDMA	Canine	Less than **18**	**18–35**	**36–54**	Greater than **54**	
	Feline	Less than **18**	**18–25**	**26–38**	Greater than **38**	
UPC ratio						
Substage based on proteinuria	Canine	Nonproteinuric **< 0.2** Borderline proteinuric **0.2–0.5** Proteinuric **> 0.5**				2
	Feline	Nonproteinuric **< 0.2** Borderline proteinuric **0.2–0.4** Proteinuric **> 0.4**				
Systolic blood pressure in mm Hg Substage based on blood pressure		**Normotensive < 140** **Prehypertensive 140–159** **Hypertensive 160–179** **Severely hypertensive ≥ 180**				3

Source: *Diagnosing, Staging, and Treating Chronic Kidney Disease in Dogs and Cats.* International Renal Interest Society. Accessed January 7, 2026. https://static1.squarespace.com/static/666b9ecb4064a156963b4162/t/66a6dbe460ba38633de536c0/1722211300466/IRIS_Pocket_Guide_to_CKD_2023.pdf

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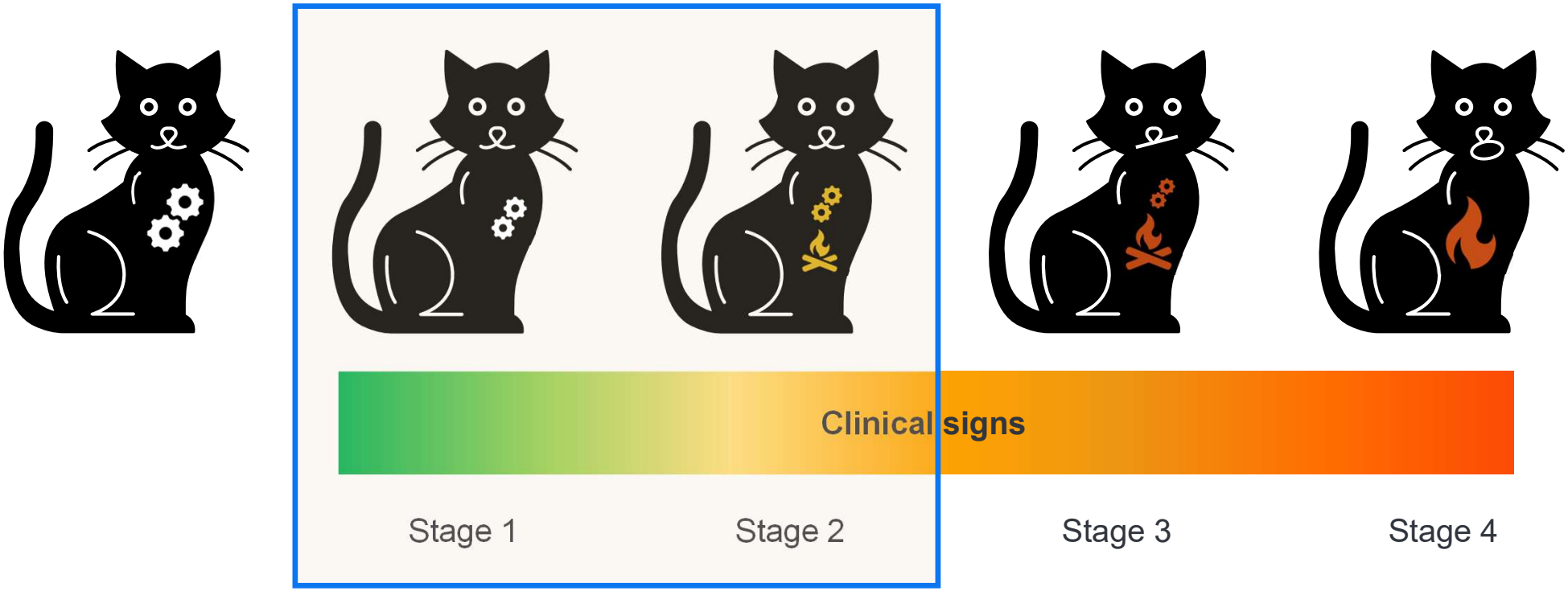
IRIS guidelines for staging CKD



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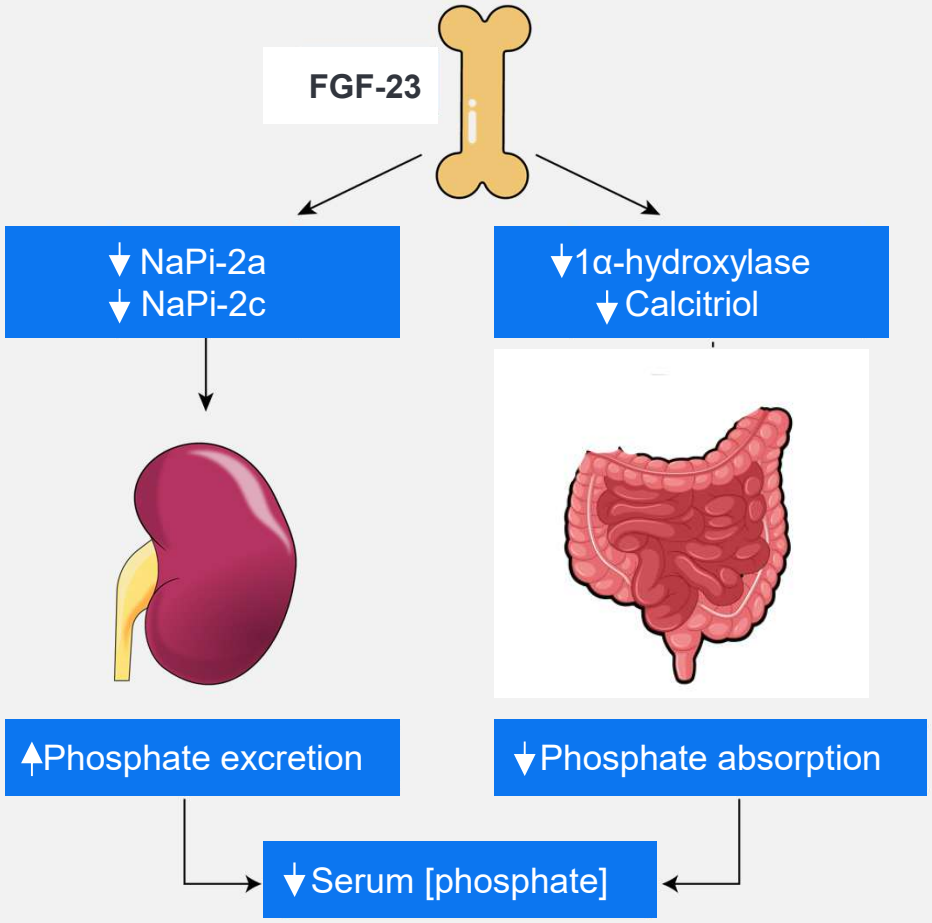
Early marker of chronic kidney disease?

Yes! Fibroblast growth factor-23 (FGF-23) is an early marker of CKD

- FGF-23 is a phosphatonin; a protein/hormone that regulates phosphate balance
- Released from osteocytes in response to increased phosphorus, calcitriol, and PTH concentrations
- FGF-23 decreases phosphorus and calcitriol concentrations
- Important in animals with chronic kidney disease
- FGF-23 often rises BEFORE serum phosphorus does
- Clinical measurement is now commercially available for and indicated for *cats* with kidney disease (impaired phosphate excretion)



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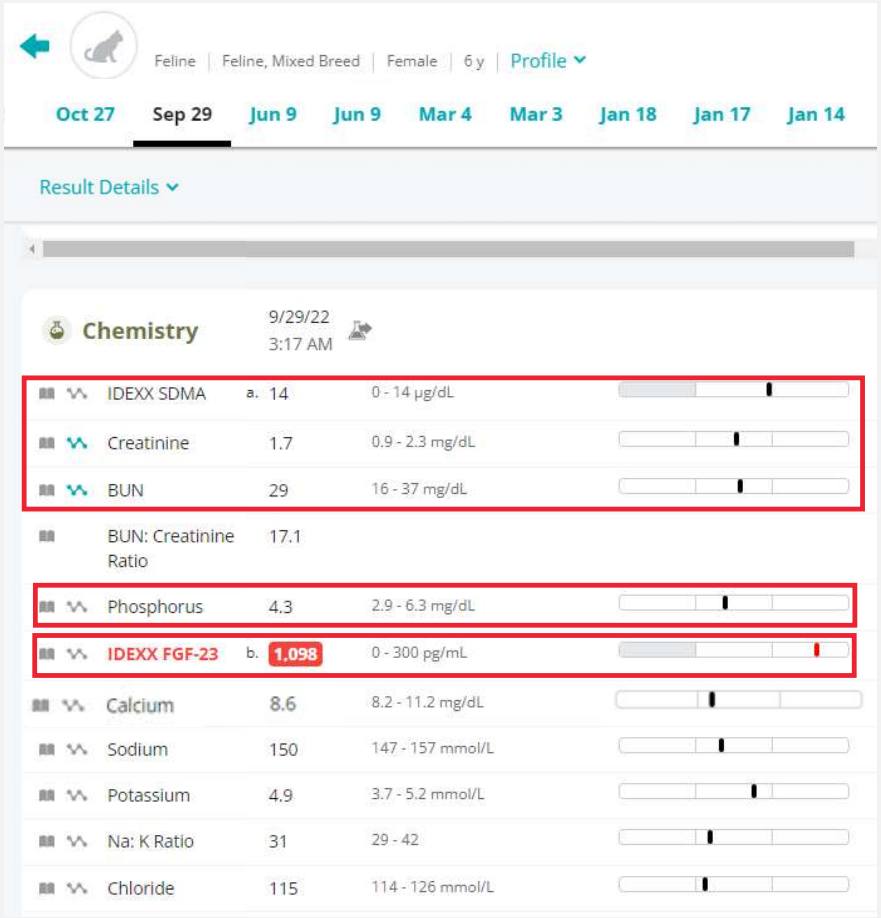
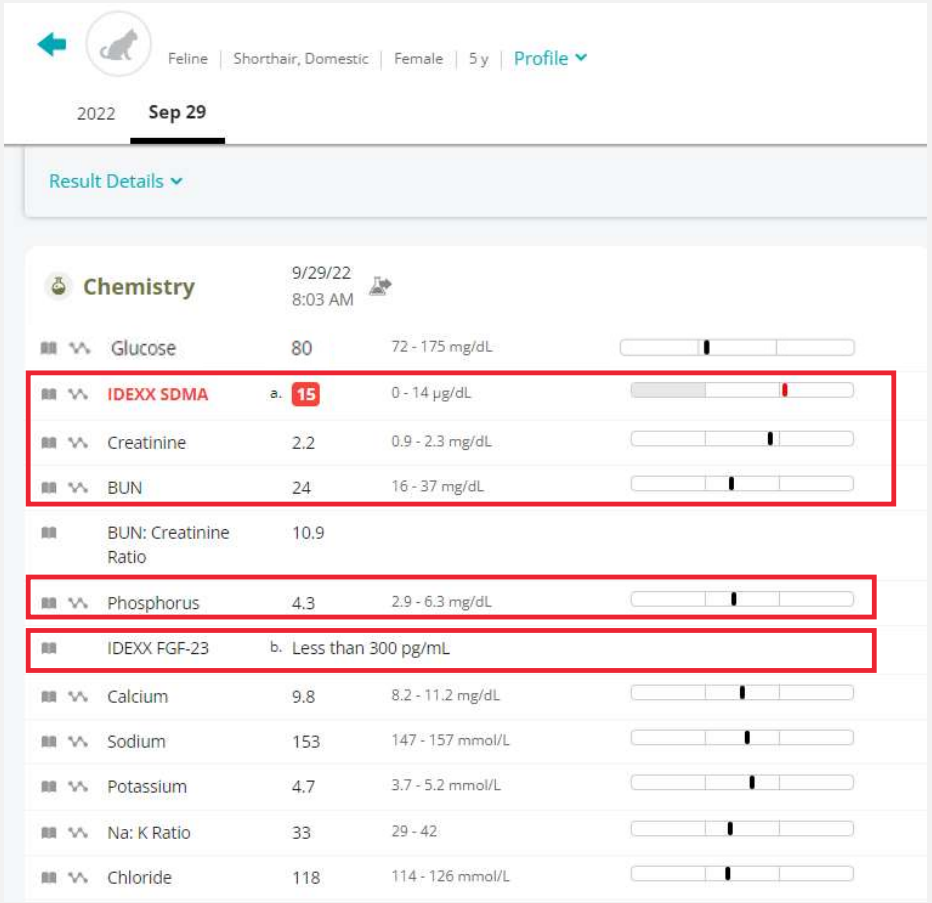
FGF-23 identifies phosphorus overload before overt hyperphosphatemia





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IDEXX FGF-23 bottom line:

Persistent Findings of CKD – IRIS Stage 1 or 2 Diagnosis

Metabolic bone disease is a complex syndrome that involves fibroblast growth factor-23 (FGF-23), parathyroid hormone (PTH), 1,25-dihydroxy D3 (1,25 vitamin D_3, calcitriol), calcium, and phosphorus

FGF-23 is released in response to increases in phosphorus and calcitriol

FGF-23 often rises before total serum phosphorus

Alerting to earlier need for phosphorus reduction

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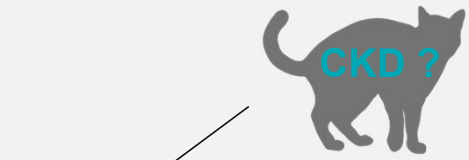
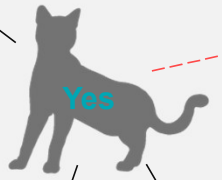
Simplified medical workflow for FGF-23 in cats with CKD



>60% of cats in their lifetime will be affected



Yes

- Persistent increase in SDMA and/or CREA
- Inappropriately concentrated USG
- Abnormal kidney imaging
- IRIS Stage 1 and 2
- Total phosphorus < 4.6 mg/dL

No

- Single increase in SDMA or limited data
- No evidence
- Recheck in 6-12 months

Normal FGF-23 or Borderline

High FGF-23

Recheck FGF-23 3-6 months

* Repeated Borderline treat as high

Targeted Therapy or increase in therapeutic control

Recheck alongside kidney parameters every 3-6 months

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Impact of renal diet on cats with early CKD:

Big Data Study

- Does early diagnosis and treatment of CKD with renal diet **slow progression** of disease in cats?
- Does early diagnosis and treatment of CKD with renal diet **impact survival** in cats?

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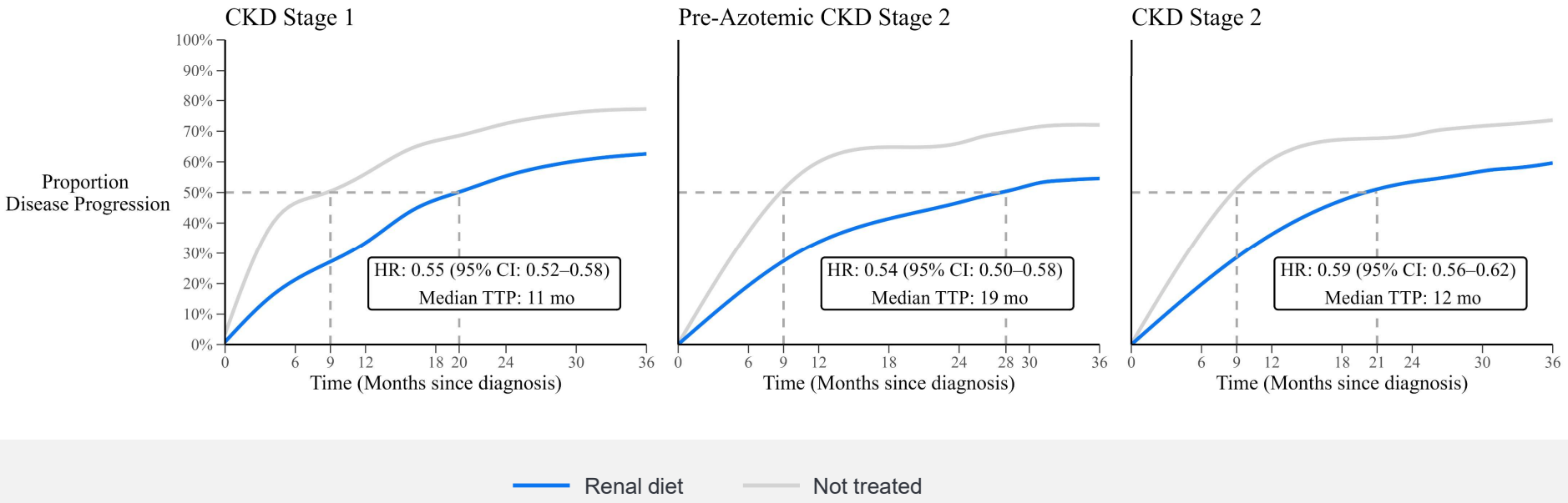
CKD cats treated with renal diet in early CKD stages progress more slowly



On average, early-stage CKD cats receiving renal diet remained in their current stage 11–19 months longer than similarly staged cats not fed a renal diet.

Source: Data on file at IDEXX Laboratories, Inc. Westbrook, Maine USA: IDEXX manuscript; *JAVMA* publication pending.

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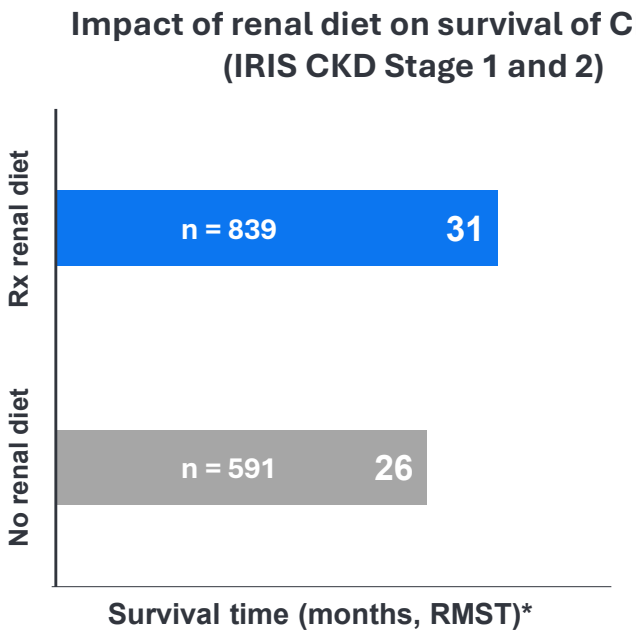
CKD cats lived longer on renal diet



Hazard ratio: **0.70** (95% CI: 0.67–0.74) *P* < .001)

Cats diagnosed and treated with renal diet in IRIS CKD Stage 1 and 2 survived 5 months longer than CKD cats not fed a renal diet.

This impact equates to an average 20% extension in survival during the 3-year study follow-up period.

Summary: Diagnosis and treatment of IRIS CKD Stage 1 and 2 cats with renal diet was associated with **slower progression** and **longer survival**.

Source: Data on file at IDEXX Laboratories, Inc. Westbrook, Maine USA: IDEXX manuscript; *JAVMA* publication pending.

*Increased survival time is calculated using restricted mean survival time (RMST). RMST is the area under the survival curve up to a specific time point and is generally more reliably estimable than mean or median survival times. All cause mortality was measured for survival analyses across a 3-year follow-up period.

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Renal biomarkers, use every tool you have!

- **Think about limitations:**
  - Creatinine: muscle mass, early disease
  - SDMA: rare comorbidities
  - Tubular injury markers: the IDEXX Cystatin B Test
  - FGF-23: comorbidities
  - USG: comorbidities and medications
  - Proteinuria: comorbidities

Even with limitations, often by using all of the available diagnostics you can put the puzzle together.

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Take Home

- Acute kidney injury and chronic kidney disease are a continuum
- A COMPLETE urinalysis is of UTMOST importance when evaluating kidney disease
- Become familiar with renal biomarkers and their indications as well as their limitations
- IDEALLY, patients at risk for renal injury or with early CKD are identified and managed BEFORE azotemia develops
- Fluid therapy paradigms have changed…dramatically.
- Newer biomarkers
  - SDMA earlier and more accurate estimate measure of GFR
  - Urine cystatin B, a *urine* renal biomarker, is a specific marker of ACTIVE renal tubular injury
  - Fibroblast growth factor-23 (FGF-23) is a marker of metabolic bone disease; it is an EARLY marker of CKD, and it is currently available through IDEXX for *feline* patients

Thank You!!

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