

The Portuguese Water Dog Foundation, Inc.®

We are dedicated to funding canine medical research focused on issues that affect the health and well-being of Portuguese Water Dogs everywhere.

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Addison's Study

Steven G. Friedenberg,
DVM, PhD, DACVECC,
University of Minnesota,
College of Veterinary
Medicine

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Please consider donating
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Our list of donors who
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UNDERSTANDING THE GENETICS OF ADDISON'S DISEASE IN PWDs

The Portuguese Water Dog Foundation is excited to kick off a new research study to investigate the genetics of Addison's disease — specifically in PWDs! The work proposed by Dr. Steven Friedenberg's research team at the University of Minnesota College of Veterinary Medicine will follow a state-of-the-art approach to mapping complex genetic traits, including collecting blood samples and pedigrees, extracting DNA and genotyping each dog. Their goal is to use this research to better understand the disease mechanism and disease triggers, and to develop a test that can help breeders decrease the incidence of the disease. The Foundation has committed to donating more than \$225,000 during the three-year study.

Addison's disease (also referred to as primary hypoadrenocorticism) is an immune-mediated disease in dogs and humans in which the body attacks the outer layer of the adrenal glands. This leads to a deficiency in key hormones (cortisol and aldosterone) which regulate responses to stress and water/electrolyte balance. Dogs often present with waxing and waning gastrointestinal signs, a finicky appetite, or generalized lethargy. In some cases, dogs present to veterinarians in a shock state, which can be life-threatening if the signs of Addison's disease are not recognized promptly. Therapy for Addison's disease is available, but requires lifelong commitment by owners with hormone replacement therapy (typically a monthly injection and daily pills).

The study will begin May 1. Researchers are actively seeking PWDs in the US and Canada who have Addison's disease, as well as PWDs over 10 years of age without Addison's disease. All that's required is a small blood sample. The study will pay for all costs, including shipping to the lab. For additional information, please check out the study website at z.umn.edu/addisons or email them directly at pwdstudy@umn.edu.

In addition to this important study, Dr. Friedenberg is also conducting a second study that he would like to open to all PWD owners in the US and Canada. This second study aims to understand the environmental exposures that might trigger Addison's disease. They are hoping owners of healthy and affected dogs of any age will participate. All that's required for the second study is a 10-minute survey that you can complete from your computer or mobile device. You can access the survey through this link https://umn.qualtrics.com/jfe/form/SV_6RPGbB7IPzap7j7. Please email dogpoll@umn.edu if you have any questions or would like to participate in the environmental exposures survey.

The Foundation looks forward to providing you with updates as we move forward with this important genetic research!

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FINAL REPORTS

Measuring Chemotherapy Drug-Resistance in Dogs with T-cell Lymphoma*Paul R. Hess, DVM, PhD, North Carolina State University*

RESULTS: New Technology Helps Detect Small Amounts of Drug-Resistant Cancer Cells in Dogs with T-cell Lymphoma

Morris Animal Foundation-funded researchers from North Carolina State University used state-of-the-art DNA technology to help detect small amounts of drug-resistant cancer cells that persist after treatment in dogs with T-cell lymphoma (minimal residual disease, MRD). Accurately monitoring MRD could provide a fuller picture of the effectiveness of different drugs and improve treatment success, quality of life and survival for these patients.

While many dogs achieve clinical remission or appear cancer-free with intensive chemotherapy, low numbers of cancer cells can still linger. These cells are thought to be the cause of eventual treatment failure. Knowing how residual cancer cells levels go up and down after treatment may provide valuable insight on the loss of responsiveness to individual drugs in multi-agent treatments over time.

To find and measure MRD in dogs with T-cell lymphoma, the team used DNA technology to pick out the cells' unique genetic fingerprints among the larger background population of normal cells circulating in the blood. The team followed eight canine patients receiving standard-of-care chemotherapy and successfully isolated white blood cells from blood draws at periodic intervals during treatment. They then harvested and decoded the genetic information and analyzed the data to find out how many copies of the cancer cell fingerprint, if any, were present in the sea of millions of different fingerprints. They found the process could readily measure minute cancer burdens in the blood at all time points sampled.

Findings from this study are an important first step toward further development of DNA technology to monitor residual cancer cells after treatment. This new information could help reduce the number of drugs that are clearly ineffective for a particular patient, providing a more tailored treatment strategy. This conclusion is supported by another finding in the study; researchers noted drugs in the standard-of-care protocol were only superficially effective in their study dogs.

A general view before this study was that most patients induced with chemotherapy that achieved a complete clinical remission also attained a complete molecular remission (i.e., MRD fell below the limit of detection). This view would predict that cells became resistant sequentially over time as each drug was administered. By early detection of this change through next-generation sequencing, it was thought that MRD-guided drug substitutions could lead to repeated reacquisition of molecular remission, thereby prolonging overall survival. However, data from this study suggests that no particular combination of standard chemotherapeutic drugs, at this intensity, will lead to this end. Rather, only intensification (i.e., higher doses with stem cell support) or the addition of some other therapy (alternate drugs; radiotherapy; immunotherapy) will be sufficient to eradicate MRD and improve outcomes for dogs with T-cell lymphoma and perhaps other aggressive cancers.

The Role of Complex Translocations Associated with TP53 Somatic Mutations for Aiding Prognosis of Canine Diffuse Large B-Cell Lymphoma*Matthew Breen, PhD, North Carolina State University*

This study involved the evaluation of canine lymphoma biopsy specimens for the presence of tumor-associated abnormalities associated with four key cancer-associated genes (MYC, BCL6, BCL2, and TP53). In a subset of human lymphoma patients, cancer cells show structural rearrangements of MYC, BCL2, and/or BCL6, meaning that the normal organization of the gene has become disrupted in the tumor. Human lymphomas also frequently show DNA sequence mutations in the TP53 tumor suppressor gene. The presence of these abnormalities, alone and particular in combination, has been shown to be predictive of a poor response to standard treatment modalities in human lymphoma patients, and provides powerful opportunities to predict prognosis in newly diagnosed patients.

We hypothesized that the same may apply in dogs.

Continued on page 8

PROGRESS REPORTS

Diagnostic Accuracy of Point of Care Analysis of Canine Urine and Plasma in Marijuana Toxicosis

Joel Weltman, DVM, Caspary Research Institute of the Animal Medical Center

Given the increase in availability of marijuana in the United States, a higher number of presumed marijuana exposures have been reported in veterinary emergency clinics. Since the clinical signs of marijuana ingestion are non-specific and may be observed in several disorders, an accurate canine bedside diagnostic test may alleviate the need for expensive and invasive diagnostic procedures in canine patients. To date, no studies have evaluated the accuracy of urine drug screening tests using non-invasive urine or blood samples in dogs. The purpose of this study is to determine the best method to diagnose marijuana toxicity in dogs in a point of care emergency setting.

Samples obtained from a total of 56 dogs with either confirmed or suspected exposure to Δ 9-tetrahydrocannabinol (Δ 9-THC) have been analyzed by both point of care and liquid chromatography/tandem mass spectrometry (LC/MS-MS). Of those enrolled, 55 (98%) were confirmed positive for Δ 9-THC by LC/MS-MS on plasma samples. Of the 56 urine samples tested, 17 tested positive using the Alere drug screen iCassette for THC, and 26 tested positive using the NarcoCheck THC Predosage test. All of the samples that tested positive using the Alere drug screen also had positive detection using the NarcoCheck test. Sensitivity, as calculated based on positive NarcoCheck urine drug screening, was calculated as 47%. The most commonly reported clinical signs in those positive by urine drug screening test included hyperesthesia (100%), ataxia (92%), and depressed level of mentation (80%); however, no physical examination parameter was predictive of a positive urine drug screening test in those positive for Δ 9-THC on LC/MS-MS. Work continues for validation of LC/MS-MS for metabolites of Δ 9-THC in canine urine samples. Results from this analysis will provide information regarding the accuracy of urine metabolites in establishing exposure to Δ 9-THC in dogs.

Targeted Next Generation Sequencing Panel for Comprehensive Testing of Vector-borne Pathogens

Rebecca Wilkes, DVM, PhD, Purdue University

We proposed to develop a comprehensive method for detection of infectious diseases of dogs, taking the guesswork out of determining which tests to use for diagnosis, and potentially improving disease surveillance because of the comprehensive nature of the test. We proposed a combined PCR/NGS method called targeted NGS, and have developed a comprehensive assay containing 488 primer sets for pathogen detection by NGS. An initial feasibility study was performed with 18 clinical samples (9 pos and 9 neg), previously tested by a collaborating laboratory for tick-borne pathogens by qPCR. This sample set represented multiple pathogens, including *E. canis*, *Babesia gibsoni*, haemotropic *Mycoplasma*, *Borrelia*, and *Rickettsiaspp.* Comparison of the results obtained with the targeted NGS method vs. qPCR resulted in a positive percent agreement between the methods of 86%; negative percent agreement of 64% (NGS was able to detect additional pathogens that were missed by original testing in 4 samples); and Cohen's kappa of 0.46, suggesting a moderate agreement between methods. The ability of the NGS method to detect additional pathogens that were missed by qPCR was expected. The discrepant samples were sent to a third lab for evaluation by real-time PCR +/- sequencing and results are pending. qPCR was not originally performed for some of the pathogens that were detected by the NGS method. This is the benefit of using a comprehensive method, such as the targeted NGS panel.

Initial specificity testing showed no interference of canine DNA with the method. Primers were specific for the tested pathogens, with the exception of cross-detection of *B. gibsoni* with primers for *Cytauxzoon felis*. However, this was easily distinguished with raw sequence evaluation.

Additional studies are required to complete the proposed aims. More characterized clinical samples (by qPCR) will be evaluated with the NGS method, to reach a total of 50 samples. Specificity

testing with more pathogens from the panel is needed. Sensitivity testing for relative endpoint detection has yet to be performed but is planned

Investigation into Diet-Associated Dilated Cardiomyopathy in Dogs

Darcy Adin, DVM, University of Florida

The study is progressing on schedule and nearing completion. Enrollment for the first part of the study is complete and a peer-reviewed manuscript describing the results has been published in the Journal of Veterinary Internal Medicine. The results of this part of the study showed higher levels for cardiac troponin I in dogs eating grain-free dog foods or foods that have peas, lentils or potatoes in the top 10 ingredients. Cardiac troponin I is a blood marker that indicates injury to the heart muscle. Even mild elevations can be important but future studies will be needed to determine with certainty that this is the case in these dogs. We did not find echocardiographic (heart ultrasound) differences between dogs eating grain-free and grain-inclusive foods. If the low-level elevation of cardiac troponin I truly indicates low-level heart muscle injury then it may be too early in these healthy dogs to manifest as echocardiographic differences.

We are also following dogs enrolled at UF that have bloodwork or echocardiographic abnormalities for a year after a diet change is enacted, to determine if any of the abnormalities will improve with nutritional intervention. We do not know if any or all of these abnormalities in these dogs are related to food and so the role of follow-up is critical to this assessment. The number of dogs being followed at this time is 17. We anticipate that this follow-up data will result in a 2nd publication. Data collection will be complete by the summer and we will then plan to analyze the data.

We will be submitting blood samples to determine if metabolic pathways in the body are different in dogs eating grain-free diets compared to dogs eating grain inclusive diets and to determine if this will change after dogs eating grain-free diets are transitioned to grain-inclusive diets. This will help us understand the changes that could be occurring in the body of dogs eating different diet types. This analysis is planned for summer 2021.

HONOR ROLL OF DONORS

Thank you to all of you who support the efforts of The Foundation. We appreciate every dollar you donate. And we still have much to accomplish. This list includes people who contributed between June and January.

Commodore \$1,000 and up

Chuck & Candi Bubert in honor of all the dogs we have loved and lost and those we now hold dear.

Janice Butler in memory of my boys "Angus" & "Zander" and all their friends we have loved and lost!

Linda K. Hunt, Kalista

Morgan Jennings

Kathy Krekow Moe in loving memory of my sweet, amazing girl, "Kylie" CH Stargazer One-Two Keep

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Victoria Trapanotto in memory of my beloved Lucia Rose (Lucy) who went to be with my Camie girl in heaven.

Tom Weissenborn in memory of Intl CH Baron, CH Ripley & Jeremy

Geri Zuckerman in honor of Seadream Portuguese Water Dogs

Captain \$500-\$999

Anonymous

Chuck & Candi Bubert in memory of precious "Luna" Aspen Coves Lunar Shadow TD THDA AWD who shared her life with Sarah Leatherman and was loved by all who had the pleasure of knowing this sweet girl.

Mary Jo Burgess in memory of CH Blackjack's Un-Frigate-Able UDX GO RN loved and missed by Gail Clark

Gary Cummins in honor of all my Portuguese Water Dogs, Kalypso, Apollo, Aphrodite (aka Aphra), Athena, Oliver & Aphrodite II (aka Aph2)

Verne Foster in loving memory of "Sloopy"

Jane Freeman in memory of "Noodle" loved and missed by Cheryl Rutz & Debbie Scott

Jane Freeman in memory of "Piper" loved and missed by Roberta Capuano & Tom Heffernan

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Sarah Leatherman in memory of the amazing 13 years of Luna and her contribution to the Shine On Project

Dr. Thomas & Mrs. Linda Majcher in loving memory of "Marlie" Sagmar's Cyclone Marlie (2005-2020)

Ann McCallum in memory of my beloved "Sophie" and "Sasha"...my hearts

Barbara & Don Niemann

John Piper & Deborah Tuttle in memory of our beloved Rosie, Rebel & Roxie Piper

June & David Poplack in memory of "Fraser" CH Eauchien & Driftwood's Fraser River

Jori Potiker

Mike & Kristi Portugue in memory of loving companions and awesome dog sport partners, "Neptune", "Ocea" & "Moby." May you rest in peace.

Linda Shooer in memory of "Leo" Oreobay Prince Of Tides

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Alison Hess in memory of all my dogs

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Dr. Barbara G. Isaacs

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The Board of the Keystone PWD Club in memory of "Miguel" CH Pennrico For The Luv Of Taylor UD NA NAJ CWDX GROM (2/15/2007-11/19/2020) loved and missed by Judy & Steve Murray

Marlene Kinkead in honor of those who love our Portuguese Water Dogs

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Portuguese Water Dog Club of Northern California in memory of "Cali" Cutwater Heart Of The West loved and missed by Barb & Ron Avila

Portuguese Water Dog Club of Northern California in memory of "Bica" Covey Runs Dream Girl loved and missed by Diana Bailey

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Nancy, Lowell & Trevor Sedlacek in loving memory of "Frisco" CH Driftwood Mirage Success' Cool Dude, and "Kellen" CH Success' Beach Baby At Sagmar

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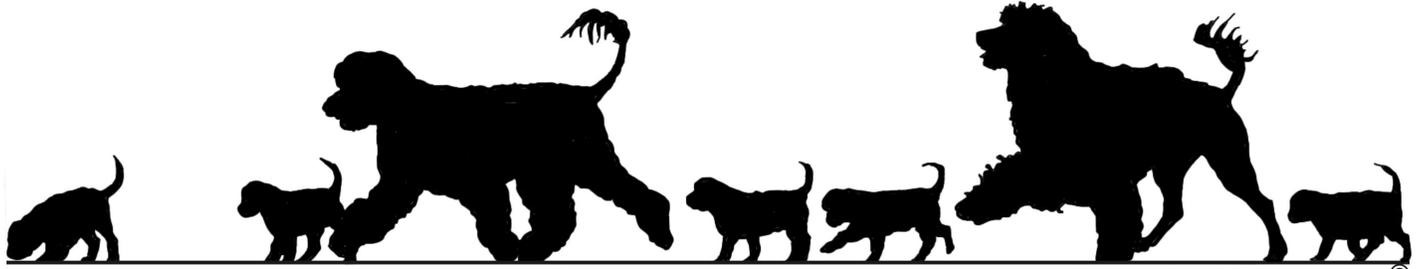
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Candi & Chuck Bubert wishing our dear friend, Sarah Leatherman, a Happy Birthday!



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Janice Butler in memory of "Elsie," a special curly girl, owned and loved by Cathy McLeod! You introduced your mom to the wonderful world of PWDs and those that love them. Miss E – you'll be missed!

Roy & Barbara Cawley in honor of Peggy Weissenborn who loved Baron, Ripley and Jeremy with all her heart!

Ellie Chiampa in memory of "Bebe" loved and missed by Bob & Leigh Pelc

Nigel Clark in memory of "Chelsea" Oreobay I Wanna Talk About Me RN OA OAJ CGC TDI and Ancient Mariner. Owned and loved by Dr. Leon Benson and Family for 15 years, 8 months and eternally.

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The Skelly Family in memory of our bright light "Chloe." We will love and miss you forever.

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Ellie Chiampa in memory of "Merlin" GCHG CH Merlin Is Magic CGC TKI loved and missed by Randy Chesnut & Marsha Tintes

Curt & Mary Conover in memory of "Libby" who is happily celebrating Christmas in Heaven this year but missing the Coniglio Family!!

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Marilyn Dickson

Lenka Ferkova in honor of the PWD PSG

Dorothy Finkelson in memory of Neptune, Ocea & Moby, and in honor of Hydro, Sprite & Splash. The best grand puppies ever!

Donna Fisher in honor of "Maya"

Fred & Susan Forman in memory of "Merlin" GCHG CH Sagmar's Merlin Is Magic CGC TKI loved and missed by Randy Chestnut & Marsha Tintes. We hope Merlin and Popeye are swapping show stories over the Rainbow Bridge.

Fred & Susan Forman in memory of "Red" Blue Run's Virgo loved and missed by Lynn Skora & Michael Hasz

Kim Gebhardt in memory of "Chili" CH MACH Benfil's Chili Pepper CD BN RN FDC MXG MJG MXF T2B CGCA CGCU TKI

Debra Giewont in memory of Leah, Inde, Ollie & Clem. The PWDs I have loved and lost and still miss everyday.

Kal Goren in memory of "T-Bone"

Valerie Grahn

Ellen & Phillip Griffin in honor of "Lita"

Linda Grubessi in honor of the PWD PSG

Melinda Harvey in honor of the PWD PSG

Barbara & Scott Henley in memory of "Beija" BOSS GCH CH Spyglass's Kissed By A Pirate WWD

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Kathryn Hug in memory of "Riggs" and "Westyn"

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Linda K. & Krista K. Hunt, Kalista in congratulations on your new titles to "Sprite" Kalista's Serendipity NA NAJ RN SIE SCE SEE TKI CGC RATO for her SCE & SEE!!

Linda K. & Krista K. Hunt, Kalista in congratulations on your new titles to "Hydro" CH Kalista To Splash-N-Dash MX MXJ RN BN CGC TKI SCM SIM SEM SBN SWN WWD RATS SROM for his SBN SWN & SEM!!

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Bill Kulhanek in honor of Dewey, Bethany & Gidget

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Carole Mclvor in memory of Deyanne Miller

Arnie Mills in memory of "Marlie" Sagmar's Cyclone Marlie loved and missed by Tom & Linda Majcher

Arnie Mills in memory of "Mango" CH Sagmar's Mango JR loved and missed by Rebecca & Joey Honstein

Mary Morehouse

Barbara & Don Niemann in memory of "Trip" Cutwater Trident Triple Threat loved and missed by Barb & Ron Avila

Barbara & Don Niemann in memory of "Cali" Cutwater Heart Of The West loved and missed by Barb & Ron Avila

Barbara & Don Niemann in memory of "Norman" Coretreale Greased Lightning loved and missed by Ann Gaskell

A. Miles & Gerry Nogelo

Terri Pecora

Pledgeling Foundation

Elaine & Chris Rasmussen in honor of the PWD PSG

Elaine & Chris Rasmussen in memory of "Artie" Avida's Artemesia Going For Baroque, with love & tears

Elaine & Chris Rasmussen in memory of "Ulisse" do Lusiadas and his brother, "Maquah" Urso do Mar do Lusiadas

Felix Rodriguez & Susan Pemberton in memory of "Cash" and "Newton"

Barbara & John Rossi in memory of "Jamie" and "Farley"

Julie Rust in honor of the PWD PSG

Nancy, Stanley & Ollie Schonberg in memory of beautiful "Chelsea," such a special girl

Pam Selvig as a Thank You to Jane Freeman for our beautiful boy "Tripp" Freestyle Chaos and Commotion Again

Harris & Bonnie Sklar

Barb Stanek in memory of "Rudy" and "Trio"

Robert & Cynthia Strouse

Richard Sweet & Fay Gallus

United Sunshine State PWD Club in appreciation of Chuck Bubert for judging at the Callaway Water Trial.

Elaine Suter in honor of the PWD PSG

Holly Trumble in loving memory of "Baxter" loved and missed by the Dorighi Family

Holly Trumble in loving memory "Rio" loved and missed by Dianne & Lynn Lippoldt

Nancy Vener

Barbara Vogelmann in honor of the PWD PSG

Mary Warner

Janis Watts in memory of "Molly Murphy" CH Legado Ousadia Menina loved and missed by Michele Murphy

Kim & Jerry Wolcoveick in memory of Alice Vicha and all the Norvic PWDs

Matt & Kendra Yociss in honor of "Taylor Belle" and "Sasha Rayne" who fill our days with joy and mischief!

Deck Hand up to \$49

Anonymous

Anonymous

Anonymous

Carol & Warren Cooke in memory of Randy Latham at Christmas

Fred & Susan Forman in memory of "Bebe" loved and missed by Leigh Pelc

Fred & Susan Forman in memory of "Frigate" CH Blackjack's Un-Frigate-Able UDX GO RN loved and missed by Gail & Richard Clark

Melinda Griffin in memory of "Allie" loved and missed by Judy Roland

Linda K. & Krista K. Hunt, Kalista in congratulations on your new title to "Beckon" Kalista Zummon With A Wave BN RN TKI for his BN!!

Linda K. & Krista K. Hunt, Kalista in memory of "Bingo" CH Sunshine's Bayshore Bonito Bingo Of Hope loved and missed by Wayne, Penny & Baily Wetmore

Linda K. & Krista K. Hunt, Kalista in congratulations on your new title to "Lyra" Kalista's Vega A Lyrae RI SWN SIA TKI for her SIA!!

Linda K. & Krista K. Hunt, Kalista in memory of "Pepin" GCH CH MACH13 PACH4 Neocles Pepin Waves Of Hope RN MXG4 MJB5 MXP10 MXPC MJP17 MJPG2 PAX4 NF T2B June 9,

2007-October 20, 2020, loved and missed by Sandy Kott

Linda K. & Krista K. Hunt, Kalista in congratulations on your new title to "Trip" Kalista's Asked 'N Answered for NADD-AKC #1 PWD for 2020

Linda K. & Krista K. Hunt, Kalista in memory of "Miles" loved and missed by Barb and Jerry Zeller

Linda K. & Krista K. Hunt, Kalista in congratulations on your new title to "Freya" Kalista's You Betcha NAJ for her NAJ!!

Linda K. & Krista K. Hunt, Kalista in congratulations on your new title to "Titan" CH MACH Sun Joy's Back In Time At Kalista RI MXB MJG MXF T2B for his MACH!!

Linda K. & Krista K. Hunt, Kalista in memory of "Gulliver" Kalista's Lovin' Spoonful, loved and missed by Caren Stanley & family

Linda K. & Krista K. Hunt, Kalista in congratulations on your new title to "Tally" GCHB CH Kalista's What A Catch RI TKI CGC WWD for her GCHB!!

Linda K. & Krista K. Hunt, Kalista in memory of "Jasmine" Lake-Breeze Jumping Jasmine CDX RE OA OAJ TKI WWD loved and missed by Cathy Shonka

Linda K. & Krista K. Hunt, Kalista in congratulations on your new title to "Tally" GCHB CH Kalista's What A Catch RI TKI NAJ CGC WWD for her NAJ!

Linda K. & Krista K. Hunt, Kalista in memory of "Question" American Dancer's She's A Rainbow RN CGC TKN loved and missed by Karen Kirby Ash

Wendy Katz in memory of "Zoey" Caladesi Captain Sea Ring. Zoey was the sweetest dog and will be greatly missed.

Amy Laden in memory of "Zach" CH Roseknoll de Chinook Noir CGC TDIA

Toni & Harry McHugh

Debbie & David Minkoff

Leigh Pelc in memory of "Merlin" GCHG CH Sagmar's Merlin Is Magic CGC TKI

David & Sonia Novick

Sandra Novicki in memory of "Sailor"

Karen & Walter Paulick in memory of Marge Schreiber

Karen Pratt in memory of "Cali" GCH2 MACH20 Cutwater Heart of the West MXC5 PDC MJS6 PJC MXP2 MJP2 FTC2 MFS3 TQX T2B16 TKA CWDX

Jeanne Rex in memory of Hunter Bubbles of Anchor Bay

Donna & John Sack in memory of "Merlin" BIS BISS GCHG CH Sagmar's Merlin Is Magic CGC TKI

Luanne Teller in recognition of Marion Liberatti's birthday

Paula Trost

Susan Vecchione in memory of my fantastic "Faial!"

Deck Hand up to \$49 continued

Jerry Weinberger in memory of "Zach" CH Roseknoll de Chinook Noir CGC TDIA
 Todd & Christine Williams in memory of "Molukie"

Marion Liberati's Giving Tuesday
 Shelly Plucker Robinson
 Anne Herberholz
 Jacqueline Seigel
 Sue Robinson

Janet Marshall
 Carol Putnam
 Stephanie Mair's Birthday
 Diana Jones-Saucida
 Diane Crews

Marlene Rebello's Giving Tuesday
 Marlene Rebello
 Viviana Cherman
 Linda Taylor
 James Vogt
 Chris Rebello
 Rosie Yandell

Facebook Fundraisers

Portuguese Water Dog Foundation, Inc.

Zech Meibaum's Birthday
 Zech Meibaum
 Susie O'Neal Peasley

Tori Passmore
 Stacey Glascock
 Brenda Stuckey

Sarah Leatherman's Birthday
 Pat Greer
 Joe Durham
 Helen Phillips
 Judy Newton
 Laura Barr

Edith Ardelean Bostina
 Alice Pryor

Kelley Dimke's Birthday
 Lorna Coloccia

Roberta Langford
 Alison Criner

Marion Liberati's Birthday

Pamela Oberst

Arnold Barrett's Birthday

Debbie Totten
 Ann Camp
 Jacqueline Seigel

Mary Jensen
 Sarah DePaoli

Jane Marchand
 Becky Smith

Sue Robinson
 Martha Ruskai

Karen Ash
 Susan Wells
 DL Crutcher

Cynthia O'Connor's Giving Tuesday
 Jen Cunningham
 Mary O'Connor

Instagram Live
 Adrian Geiser Dempsey

Patty Hobin

Linda McElwee's Birthday

Anne Wagner

Glassybaby Fundraiser
 Laurie Matthews

Becky Hawkins
 Jerry Heftler
 Teri Murdock

Jean Hassebroek
 David McElwee
 Linda McElwee

Rita Araujo
 Margaret O'Connor

Aiding Prognosis of Canine Diffuse Large B-Cell Lymphoma (continued)

We tested this hypothesis using a cohort of canine lymphoma cases that were all treated using standard of care chemotherapy protocols, for which the disease-free interval (DFI) and outcome is known. The aims of the study were to establish a) whether canine lymphomas exhibit abnormalities in these genes and b) to assess whether the presence of one or more of these abnormalities in a tumor specimen is associated with the clinical course of the disease for that case. We screened the cohort of canine lymphoma cases for structural and numerical abnormalities involving MYC, BCL6, and BCL2. Overall the data suggest that rearrangement of the genome at the MYC and BCL6 loci is relatively rare within any given case. The frequency of MYC rearrangement in dog lymphomas (19% of cases) was similar to that seen in human cases (10-15%), while BCL6 rearrangements were less commonly observed in dog versus human cases (18% and 30%, respectively, Li et al. 2018). Furthermore, 50% of dog cases showed an increase in the number of copies of the MYC gene in tumor cells, compared to normal controls. In contrast, while BCL2 rearrangements are found in 20-30% of human lymphomas, this abnormality was detected in only 2% of dog tumors. Interestingly, however, dog cases harboring this rearrangement were among the poorest responders to chemotherapy, with a DFI of 38-42 days, compared to a mean of 250 days across the cohort. Furthermore, one case with BCL2 rearrangement was the only case found to also exhibit rearrangements of both MYC and BCL6. In human lymphomas, this combination is termed a 'triple hit', and is associated with a particularly poor prognosis.

DNA sequence mutations of the TP53 gene were also infrequent among dog cases. As in human patients, the majority were located in exons 7 and 8 of the TP53 gene. Of the mutations observed, 87% were predicted to have a deleterious impact on the function of the gene, suggesting that they play a role in tumor pathogenesis rather than being coincidental events. Adding further support, four of the mutations have been identified in prior studies of dog lymphoma. Additionally, the dog counterpart of the three most frequently affected sites within human TP53 were represented as mutations in our canine lymphomas. Interestingly, no TP53 mutations were found within the subset of dogs whose tumors responded well to chemotherapy, and MYC was the only one of the four abnormalities to be found in good responders.

Statistical analysis of these findings showed that cases with mutation within TP53 exon 5-8 mutation were more at greater risk of responding poorly to standard of care chemotherapy compared to those cases in which no mutation was detected. Similarly, cases with BCL6 rearrangement were at greater risk of responding poorly compared to cases in which this alteration was not detected. No significant correlation was evident when considering MYC alterations, while the incidence of BCL2 rearrangement within the lymphoma cohort was too low to permit statistical evaluation. Interestingly, combinatorial assessment showed that there was no compounding effect associated with the presence of both TP53 exon 5-8 mutation and BCL6 rearrangement. Instead, the treatment response of dogs with tumors bearing both these alterations was comparable to that of those with TP53 exon 5-8 mutation only, although the significance of this observation was lower due to the small number of cases with both alterations. Analysis of additional cases will aid a more complete understanding of the clinical relevance of cases with alterations of both genes. Further investigation will also be required to determine whether TP53 mutation and BCL6 rearrangement are predictive of therapeutic response for other treatment regimens, and to develop these findings into a tool for application to newly diagnosed cases in a clinical setting. Continued investigation will also be necessary to establish whether TP53 mutation and BCL6 rearrangement are predictive of therapeutic response for other treatment protocols used for canine lymphoma, and to develop these findings into a tool for application to newly diagnosed cases in a clinical setting.