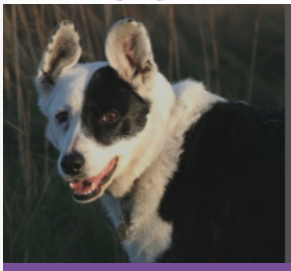


ONCOALESCE

Monograph

#4 December 2022

Greetings!

Dear Shah,

Nurturing new additions

Welcome to the forth edition of the Oncoalesce Monograph. I do hope that you had a pleasant Thanksgiving holiday with friends and family.

I have left the climbing metaphor for a new, equally shoe-horned metaphor allowing me the opportunity to feature the latest addition to the Shah household - "Juniper Scruffles". As with (very sharp) kittens, we should be nurturing the new additions to veterinary oncology - supporting them where we can as they develop their full potential. (Sadly, genomics, though very important to our future, is not quite as cute as Juniper!)

This edition takes a deeper dive into how we can trust and utilize genomics, specifically in osteosarcoma with Vidium. We also explore the potential for genomics in helping to predict chemotherapy response in lymphoma with ImpriMed

In case you missed them in Norfolk, there is an introduction from the new Canine Health and Registry Exchange - Take CHARGE", with support from Jaguar Animal Health.

Nutramax Laboratories provide an update on Denamarin providing support with liver toxicity and further discussion on Sulforaphane including potential support with chemotherapy induced cardio-toxicity.

There is an announcement from Elias on new apheresis sites and a new clinical trial in Lymphoma, and an announcement from ImpriMed of their improved performance CHOP prediction model.

Finally I asked the panel for any take away useful notes from VCS and they provided some reminders.

Several people have asked me for a PDF of the monograph, making it easier to read/transport/print for the plane etc. Please email me if you would like the PDF version.

I know it is a few weeks away yet, but happy holidays! There is plenty of material brewing for February's edition. I hope you like it,

Tariq

Email me!

Disclaimer and stuff

The following notes have been taken directly from data presented to the panel of oncologists in the Oncoalesce meeting #4. They then contain direct quotes and questions from the panel as well as the answers provided to them by the companies.

It is important to note some views presented here are made by individual oncologists but are not necessarily representative of the whole group. Whilst the panel comments are direct quotes, they are anonymized.

Conflict of Interest: All members of the panel were paid for their time by Oncoalesce at an industry acceptable hourly rate. They were not paid any other monies and act independently from the companies represented.

Panel (not all are present at every meeting):
- Dr. Jeff Bryan - University of Missouri
- Dr. Kim Cronin - MA Veterinary referral hospital
- Dr. Pamela Jones - QBiotics
- Dr. Kendra Lyons - In-between
- Dr. Melissa Parsons-Doherty – Pearland Animal Cancer and Referral Center
- Dr. Erin Roof – Animal Cancer Care Clinic
- Dr. Aarti Sabhlok – Ethos Pet Emergency and Specialty Ctr Marin
- Dr. Andrew Vaughan – Las Vegas Veterinary Specialty Center
- Dr. Rachel Venable - Pet Cancer Care Consulting
- Dr. Carissa Wood - TOC Oncology

Companies
- Elias Animal Health
- ImpriMed
- Vidium Animal Health
- Jaguar Animal Health
- Nutramax Laboratories

There are at least 24 companies with an active presence within veterinary oncology. I hope over time more companies will be represented through Oncoalesce and will use this platform to provide clinically relevant information for you to be able to trust and adopt.

ELIAS®
ANIMAL HEALTH

Update

New ECI-Lymphoma trial to be initiated this quarter.
B-cell lymphoma patients will be initially treated with SOC chemotherapy. Once in remission, patients will be treated with the Elias immunotherapy protocol.
Single site study (Dr. Anne Jeglum, West Chester, Pa.)
Readouts: PFS, survival at 18 months and overall survival
Additional sampling anticipated include cancer tissue genomics analysis and tracking of ctDNA in these patients

New apheresis location in the Midwest
We continue to expand our apheresis accessibility to clients and clinics with a new service locations at:

MedVet in Columbus, Ohio
Iowa State University, Iowa

IMPRI MED

Update
Announcing ImpriMed's Next Generation of AI Models for CHOP Therapy Outcome Prediction (v2)

ImpriMed is thrilled to announce that, on November 1st 2022, we upgraded the CHOP therapy section of our Personalized Prediction Profile with more powerful artificial intelligence (AI) models and an easy-to-read report format that provides faster access to critical information.

Our CHOP prediction report provides you with the likelihood that your individual patient's cancer will go into complete remission (CR) after different durations of CHOP therapy and the longevity of the remission that your patient is likely to experience. Caregivers can use these predictions to tailor treatment to individual patients by deciding if CHOP therapy is the right option and how long to administer CHOP before exploring alternatives.

Predictions are generated by AI models trained to forecast real-world clinical outcomes collected from naive canine lymphoma patients who underwent CHOP or L-CHOP therapy. Thanks to our ongoing collaboration with the ImpriMed user community, these outcomes now include an expanded dataset of 174 canine lymphoma patients. Our AI predicts these outcomes using multiple sources of patient information, including drug-sensitivity testing, medical history, flow cytometry metrics, and clonality testing.

The Discussions

vidium ANIMAL HEALTH a TGen subsidiary

Brief Update on SearchLight DNA REPORT

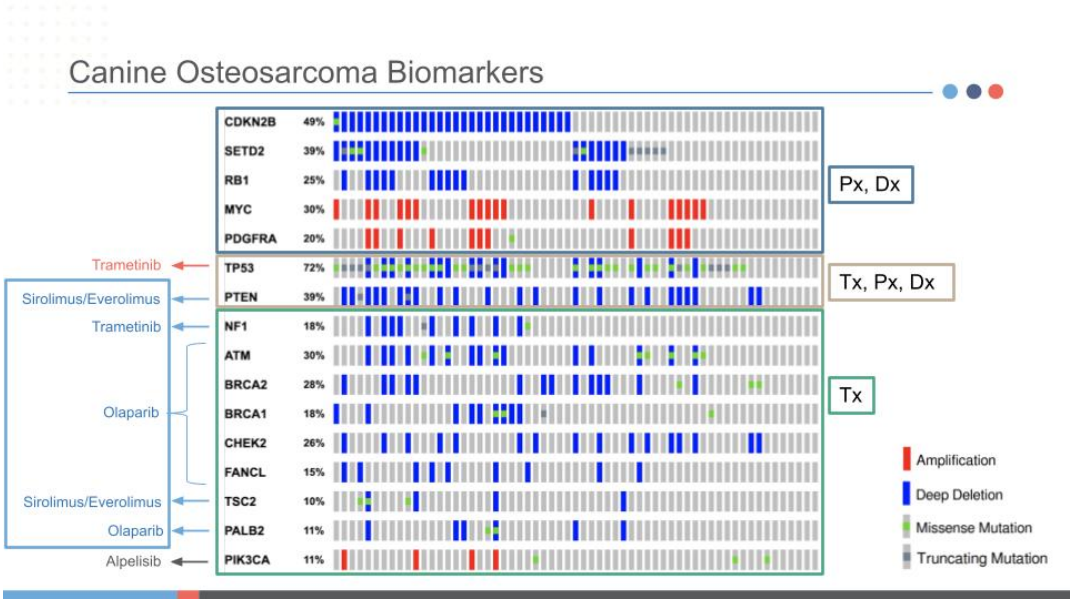
We've launched a NEW REPORT VERSION that is much more digestible and readable. It has all the same valuable information as the old report, but with some key changes:

- The first 2 pages should tell you all the genomic findings for the patient.
- We show the EVIDENCE LEVELS for each mutation's biomarker association (with diagnosis, prognosis, therapy) RIGHT ON THE REPORT (ie. you don't have to sift through the variant summaries to get this information; you can see it all on page 2 of the report, all with one quick glance).
- All the information that was previously on the old report is still there, but a lot of it is now hyperlinked (such as the gene summaries and clinical trials).

OSTEOSARCOMA: Why would you think of SearchLight DNA for these cases?

In a cohort of 65 osteosarcoma cases that were evaluated by SearchLight DNA, there was **clinical actionability in the majority of cases**. For therapeutic actionability alone, **>70% of cases matched to a targeted therapy.**

Matching targeted therapies included **olaparib, sirolimus, and trametinib**, all of which are available through compounding pharmacies. Below is an oncoprint of some of the frequently mutated genes found in this cohort of osteosarcoma. Matching targeted therapies are to the left; Biomarker associations are to the right.



- Dx = Diagnostic biomarker, Px = Prognostic biomarker, Tx = Therapeutic biomarker
- Blue font in blue box on left indicates drugs *available* to vets from compounding pharmacies
- Red font indicates a *resistance* (not sensitivity) association.
- Gray font indicates that it is *not yet accessible* by vets from compounding pharmacies

Thoughts on the presentation:
Very helpful summary of changes to the report; I particularly like that the evidence level is now right on the front; a lot of the bulk (although necessary information!) made it very difficult to read through. I also appreciate the information about osteosarcoma!

Thank you. We wanted to make this report as user-friendly as possible, and I am glad our new report version is achieving that goal.

The science behind this is exciting and I am glad to hear that there is additional work being done. I find that the ability to use this testing for prognostic, diagnostic and therapeutic information is interesting.

Thank you. SearchLight DNA's value outside of therapy is an area we want to emphasize, so we appreciate your notice of it.

I agree; I saw an example of the new report at VCS and it is much more digestible clinically but still includes the science/data information.
We all realize that there has been very little improvement in the treatment of OSA over the last three decades and exploring the potential for targeted therapy is intriguing and necessary.

We are going through some of the major cancer types that we see in veterinary medicine. Osteosarcoma is our second one. More to come on that front soon.

The readability is improved and I do appreciate the evidence levels and association with Px and Tx.

Thank you for your feedback. I am glad the evidence levels are coming in handy.

Questions (concerns and clarification)
Were the OSA samples cytology or histopathology out of curiosity and did they look at metastatic lesion at all?

The OSA samples were from histopathology and primary lesions, with the exception of 1 sample which was from an aspirate of a metastatic lung lesion.

I still have concerns about whether or not treatment for the actionable mutations is going to be effective given that cancer is a complex set of mutations and that we do not know if these are the driver mutations and also if there are other mutations that interact with them. I also have the concern that we will find that there will be an issue with resistant to the molecules in the future so that we still need to look at combination therapies.

Thank you for your comment, and I appreciate your concern. Canine cancer driver mutations are increasingly well-understood based on primary canine data. We bring that information to each report. We've also lifted over the wealth of data on human driver mutations to the canine genome so that we can bring that to bear as well. We bring all of this peer-reviewed annotation to each report in our rigorous evidence-level framework such that these assessments can be made on an individual basis for each dog with strong data support.
In addition to this evidence-based annotation of a mutation's driver status and biomarker value, we also leverage individualized review of the patient's genomic data and pathologic sample assessment behind the scenes to guide mutation interpretation and prioritization. For example, the mutation allele frequency and copy number depth are two features of the genomic data that, in concert with understanding the estimated tumor content present in the sample based on pathologic review, guide our assessment of the role of each mutation in an individual case.
Ultimately, I agree that there is concern for resistance with single agent therapy, as we experience with cytotoxic chemotherapy. Therefore, combination therapy – of different targeted therapies with each other as well as with other therapeutic modalities – will likely be more promising. I look forward to studies that can prove this and better inform combination therapy. In the interim, I do advise that we exercise copious caution when combining therapies, since safety is a top priority with our patients.
I am happy to see more and more clinicians with our similar mindset, eager (and even starting) to combine targeted therapies either with each other and/or with other cytotoxic chemotherapy and even other therapeutic modalities (such as radiation therapy and immunotherapy).

Is there any way to know if any of these biomarkers are being overexpressed? I am just thinking that if we knew which biomarkers are being over expressed/upregulated then those could be the markers to use the specific targeted therapies and help to narrow down what targeted therapy to use.

Due to the increasing number of clinicians requesting this information, we are now including prioritization of the mutation with the matching drug in the SearchLight DNA summary. Hopefully, clinicians will find this information helpful to have directly in the report. Of course, we are happy to elaborate with a (complimentary) consultation if requested.

Any Experiences with this or similar offerings

I have used Searchlight once and found the information to be very informational particular since it provided some level of the use of a platinum drug in my patient. I also like the information in regards to what we know about prognostic factors in dogs and humans and there is information about whether or not the mutation affects prognosis in that particular type of cancer.

I am glad that SearchLight DNA has been helpful for you.

I have used it on some hemangiosarcoma and other odd tumor cases, but it was still challenging to know what targeted therapy to use and how "bad" the prognosis was when we already knew it was not a good prognosis.

Thank you for your comment. We are now including prioritization of the mutation with the matching drug in the SearchLight DNA summary so that it can give the clinician more guidance on what drugs to consider with higher priority.
For the prognosis piece, we should get more and more of that data as we are actively collecting and analyzing real-world outcomes, so please fill out our outcome surveys or send your patients' records if you haven't already done so. Our goal is to get more granular with prognosis (such as be able to provide PFIs and OSTs) for patients with those mutations in their tumor.

Thoughts for the future
Are there any plans to set up a good working relationship with the reference labs? I have heard that getting samples sent from the reference labs to Vidium can be challenging and very time consuming (especially if the original sample was submitted by the rDVM) and factors into our decision about which genomic profiling service to use. If they could help with the sample acquisition we could really start running with getting cases to them. Really it's about implementation into the clinic setting. If there are too many steps and time spent on the phone for nurses and doctors for logistics then I have concerns, despite great work and data, this will never take off or be utilized as frequently.

Thanks for this question. I understand the concern, but over the last year we have addressed this to ensure it should never be an issue which would get in the way of using Vidium.
We have agreements with all major labs that allows us to facilitate retrieval of samples for our clients, doing all of the legwork and making this a streamlined and easy process. We recently partnered with Antech to give clinicians the ability to order directly through this reference laboratory as well.
Not only does Vidium have working relationships with each of the major reference labs, we have designed an ordering process that makes this part completely hands off for the clinician. Once an order is placed for SearchLight DNA on Vidium's website, Vidium's customer service team takes care of contacting the reference lab, obtaining any necessary authorization signatures from an rDVM, placing the request for the sample, and even paying for the shipment of that sample to our lab. The ordering clinician does not need to worry about or participate in getting the sample to us, and there are no added fees for this service. Simply tell us in which lab the sample is (this is one of the order form questions), and we take care of the rest. You'll get an email update once your sample arrives at Vidium's lab. Veterinarians are too busy to be expected to jump through hoops transferring samples, which is why Vidium takes on the responsibility and the expense of the entire process.

My experience was that it was very easy to get the samples to Vidium but I sent my sample at the end of September (last day of the free sample!) and there may been improvements made by then. I am interested in this product for not only treatment recommendations but also for prognostic and diagnostic information and would like to see this portion of the report grown.

It's great that you had an easy experience with us. Exceptional customer experience is one of our top priorities, so it's great that you are experiencing what we intended. Since all of our biomarker associations (diagnostic, prognostic, therapeutic) are derived from published literature, our prognostic and diagnostic information will grow alongside studies as they get published. If there are other ways you'd like to see these sections developed, please let us know. We are always open to constructive criticism to make this test as user-friendly and clinically applicable as possible.

Any attempt to gain clinical insight into the usefulness of these prognostic markers – ie; if expressed, decrease survival time regardless of therapy (similar to early insights with ALP in OSA).

We are currently collecting and analyzing real-world outcome data in the hopes of answering that exact question and are excited about what we are seeing so far. Please stay tuned.

Is there anyway Vidium can look back at their data and find time frames from the listed prognostic markers? Example a dog from this OSA cohort with a negative prognostic marker; does it mean survival is 3 months vs 10 months?

We are currently collecting and analyzing outcome data in the hopes of answering that exact question too. Please stay tuned. We are also developing prospective studies and collaborations to address specific clinical questions, so please let us know if you'd like to collaborate with us in answering any specific questions you might have.

I've used sirolimus in many OSA cases with minimal success but maybe I'm not choosing the right cases or should be looking at different drugs. SearchLight would allow me to identify the best cases for targeted therapy and which ones to choose.

I agree and thank you for bringing up your experience with sirolimus in OSA cases. In the scenario where sirolimus (or any targeted therapy) is given agnostic of genomic mutations, one reason for an unfavorable outcome could be that the target is not present in that patient's tumor (similar to what was discussed in the publication by LeBlanc et al. in *Clinical Cancer Research* in 2021). I agree with you that SearchLight DNA could allow you to identify the best cases for targeted therapy and inform which targeted therapy to use, and I hope that you will consider SearchLight DNA for your OSA cases in the future.

Link to drug Monographs

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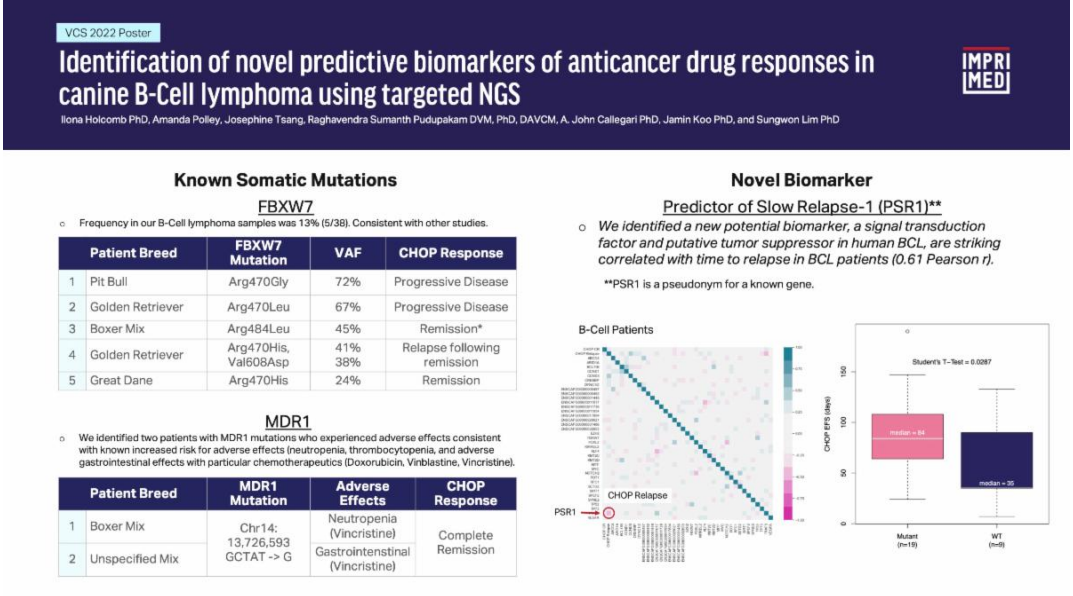


Identification of novel predictive biomarkers of anticancer drug responses in canine B-Cell lymphoma using targeted NGS

Note: this is a Proof of Concept trial to demonstrate a future direction

ImpriMed is dedicated to research into new areas and technologies to empower our machine learning models for cancer care. ImpriMed presented the results of a pilot study using Next Generation Sequencing to identify biomarkers of drug response for canine B-cell lymphoma.

Introduction

Patients with the same cancer diagnosis may respond differently to anticancer drugs. ImpriMed helps clinicians find effective treatments by providing personalized clinical outcome predictions for commonly used drugs. Our predictions are generated by artificial intelligence (AI) models trained on clinical data and functional and molecular biomarkers. ImpriMed's pilot study, presented here, was designed to increase the power of ImpiMed's commercial AI models for canine B-cell lymphoma (BCL) using NGS technology.

From ImpriMed's biobank of 1,000 paired tumor/normal canine lymphoma DNA samples with known clinical outcomes, we selected 48 patients for a pilot study. Mutation profiles were generated for each patient using targeted NGS of 578 genes selected based on their association with cancer.

Identification of novel biomarkers associated with relapse

ImpriMed's R&D team identified 377 variants/patient on average (71 somatic, 306 germline), including known BCL-associated variants like FBXW7 (13%) and MDR1 (4%). Genes were ranked by degree of correlation with clinical CR induced by CHOP therapy and by time to relapse after CHOP. Multiple novel candidate biomarkers were identified in this study, including a gene the team referred to as Predictor of Slow Relapse-1 (PSR1). Variants in PSR1, a signal transduction factor and putative tumor suppressor in human BCL, are striking correlated with time to relapse in BCL patients (0.61 Pearson r).

ImpriMed's new cancer gene panel and NGS pipeline, used in conjunction with our clinical outcomes database, provide a powerful platform for identifying novel predictive biomarkers of the anticancer drug response. This platform is now being used to collect additional data for more powerful commercial AI models.

Thoughts on the presentation:

Is this simply informative of the new upcoming parts to their panel that they are working on

The purpose of the presentation (taken from the VCS poster abstract) was to make the veterinary cancer community aware that ImpriMed is starting to investigate the use of NGS to identify biomarkers and present some of our very preliminary findings. As a "pilot" study, we don't yet have a full understanding as to how it will

impact our predictions of drug response.
We are very excited about our large retrospective validation study, which we are currently working on and includes 200 patients, 400 paired samples that includes 200 tumor samples and 200 matching normal samples. We will look to see if we can confirm our preliminary findings and find additional interesting biomarkers. Once we have the much larger retrospective study completed, we will know if certain biomarkers are useful either on their own or as part of our AI models of drug response. We can then conduct prospective studies to validate the efficacy of the biomarkers identified in the retrospective study.

Rather than looking at chemotherapy sensitivity assays which are still controversial this suggest that you can now look at genetic mutations that are known to be associated with the prognosis. I feel that this is closer to the human model which often relies more on looking at genetic changes to predict response to treatment. If this is validated for use in our patients, then it may provide information for owners to help make decision about whether to treat or not.

You made some very good points. The human model of drug response is indeed increasingly reliant on genetic alterations. At this point, we are being open minded about how our results (when we run the much larger study to get better statistical power to identify biomarkers of drug response) will be used. Because we are an AI company who has made significant advances in drug predictions using our AI in combination with our chemosensitivity assays, this NGS study of genetic alterations/mutations is intended to compliment our existing technologies and strategies.
However, our larger goal is to provide better indicators or predictions of drug response to the patients we help oncologist make treatment decisions for. Thus, we will use any important information from our genetic studies to help oncologists whether or not it is part of our AI model or a stand-alone genetic marker of response. Our new Director of Biosciences has a human cancer and NGS background, so we could not agree more that this is closer to how cancer biomarkers and treatment are addressed for humans. We are trying to bring the ability to make treatment decisions, that is increasingly common in human care, to canines to empower the treatment for veterinary oncology.

Interesting to see genetic mutations and how those can be associated with response.
We always try to innovate and improve. We feel that this powerful technology, NGS, is a great step forward.

I'm happy they are utilizing their samples and data for this next step in genomic analysis and potential biomarkers. It will be great to see how we can use this in the future

Questions (concerns and clarification)
How did they pick the 48 patients? Did the patients with the PSR1 take longer to relapse when treated with traditional CHOP?

Our intent was to just pick a small subset of patients that represented our broader population i.e. breed, gender, B-cell and T-cell lymphoma, and stage.
The patients with PSR1 mutations had longer “Event Free Survival” after successful CHOP than patients who did not have the PSR1 mutation. Moreover, time to relapse after CR was achieved with CHOP negatively correlated the presence of mutated PSR1. We need a larger study to validate these findings or if there are any specific mutations of PSR1 that better predict the length of PFS after successful CHOP therapy.

I'm worried the clinical outcomes database- given that it is representative of our non- controlled cases, is not accurate information with extreme variables and factors that will influence the AI algorithm negatively

We assume you are specifically worrying about our AI models for CHOP response and prognosis predictions (rather than single drug response predictions) as not all the vet oncologists follow the exact same protocol and the patients’ immunophenotypes are different. This is a great point, and this is why our team works very hard to collect as many clinical outcome cases as possible and very carefully establish our patient selection criteria for AI model building. Among the 3,300 cases we've served, we collected clinical outcome data from about 1,200

patients and selected 243 patients for the CHOP model development. We won't provide our CHOP prediction reports for patients with atypical immunophenotypes until we collect more treatment outcomes for these rare cases to build separate AI models.

Can we utilize expire medium tubes?

Please do not use expired media tubes as expired medium could compromise cell health and possibly influence our assays. We are happy to provide fresh media tubes. Please just request them online at imprimedicine.com/vetportal

Should we not be utilizing for T-cell cases or suspected T-cell cases?

You can submit samples from T-cell or suspected T-cell cases. We provide our single drug response predictions for any immune subtypes and CHOP prognosis predictions for naive B- or T-cell cases.

Why will they not provide CHOP predictive models for atypical B-cell subtypes?

Our AI models are built by training with patients' real-world clinical outcomes. For CHOP model development, we were able to collect a sufficient number of typical B-cell, T-cell, and T-zonal lymphoma. However, for other immune subtypes including B-ALL, B-CLL, T-ALL, T-CLL, immature B-cell, chronic myelomononcyte leukemia and DP T-cell, we need more cases to build predictive AI models. Currently, in these cases, you will still receive single drug response predictions, PARR results and flow cytometry results, just without CHOP prediction results.

Any Experiences with this or similar offerings
I haven't used the CHOP time to relapse graphs as often as the chemosensitivity response prediction (mostly because I'm using it in the context of relapsed or atypical disease, where I wouldn't necessarily be using CHOP anyways)

We are providing our CHOP response and prognosis predictions only for naive B- and T-cell patients, which aligns well with how you use our reports. We are in the process of building other CHOP models for long-term relapsed cases (5-6 months post a complete CHOP protocol). We hope the upcoming models will be helpful!

I'm currently offering to all new lymphomas and adjusting their treatment protocols based on the sensitivity results if one of the drugs is much higher than the standard CHOP drugs and the change makes sense.

Fantastic!

I have not been using the ImprMed assay at this time given that I feel as though there are limited number of other options for treatment beyond the standard CHOP protocol. Although there is information to suggest that the CHOP time to relapse graphs can be helpful, we only have limited information regarding whether selecting other drugs that appear to be better actually improves overall survival or whether these dogs are still going to have a more limited prognosis due to the nature of the tumor. I do wonder if there may be a link between the genetic mutations that predict response to treatment and the chemotherapy sensitivity assays.

Our second paper (Koo et al., Veterinary Sciences 2021) showed that our AI models accurately separate CHOP-treated lymphoma patients into a longer PFS group and a shorter PFS group. Based on the study result, we have recently developed the second generation of our AI models that predict response and survival of the naïve patients following the (L-)CHOP chemotherapy as a first-line treatment (link below). We presented at the VCS Mid-Year Conference 2022 that the higher concordance group (received 2 or 3 treatments in the top 3 of ImpriMed's AI predictions) doubled the overall response rate compared to the lower concordance group (received 0 or 1 treatments in the top 3 of ImpriMed's AI predictions) in relapsed B-cell lymphoma patients. Beyond these results, to measure overall survival, we need a long-term follow-up study. We agree with you – we also hope genetic information might be a powerful tool to help inform treatment decisions when combined with our AI technologies.
https://www.imprimedicine.com/updates/announcing-imprimeds-next-generation-of-ai-models-for-chop-therapy-outcome-prediction-v2

Are Oncologists seeing the value to aid in treating at least the atypical disease patients and some in all new lymphomas - what up-front cost does this add and have you found a significant difference in time to relapse, perhaps savings in drug costs by “choosing” more accurately?

We have been receiving good feedback on relapsed cases. The up-front cost of using our service for pet owners largely varies depending on a hospital’s margin [redacted]. As our prediction is optimized to improve patients’ clinical outcomes, a highly ranked drug may be more costly than a low rank drug. Also, as we extend a patient’s lifetime, continuous monitoring and treatment may result in more expenses. However, we can reduce the cost of the drugs that may not work, which significantly impacts the patient’s quality of life during the treatment of their cancer. In our first paper (Bohannan et al., Veterinary and Comparative Oncology 2020), we showed that use of the drugs with high ImpriMed prediction scores significantly reduces time to achieve clinical remission.

I recommend it often. I still start with CHOP unless the dog is not responding well and have switched to other drugs recommended by ImpriMed.

Thanks for understanding the value of our service! Similar to you, many doctors immediately find the next treatment option(s) right after CHOP fails.

I have no experience with the targeted NGS per se but continue to offer the Prediction Profile to naive and relapsed cases. I've modified a few protocols given the results. The phenotyping comes back timely before the next visit to help guide treatment and prognosis

We hope addition of our NGS data to our AI models could provide you more useful and accurate prediction results.

Thoughts for the future

I would like to see if the use of the assay helps us treat new lymphomas more effectively by adjusting their protocols as well as to helping when patients relapse to check that their sensitivity profile does not change leading to better responses and long term outcomes. Another thought is whether or not utilizing the prediction in relapsed cases and potentially consider either maintenance in those that may relapse earlier or simply monitoring at an increased interval rate.

For naive patients, we’ve seen many doctors using our service to help make decisions in the first-line treatment. Some doctors modify CHOP by substituting doxorubicin with mitoxantrone when mitoxantrone shows a high prediction score while the patient is experiencing cardiotoxicity. Some other doctors modify their CHOP treatment by substituting vincristine with vinblastine when vincristine shows a low predictive score while vinblastine shows a high score. In addition, doctors use Tanovea with or without doxorubicin as an alternative to CHOP when response and prognosis for CHOP are predicted to be poor but Tanovea and doxorubicin show high prediction scores.
We presented an example of long term sequential use at ACVIM, where the oncologist had been treating the patient based on the ImpriMed prediction results when the patient was naive and whenever the tumor relapsed -- 4 times in three years. Yokie is still in remission and healthy.

I feel as though this may be the direction that we need to go in rather than looking strictly at chemotherapy sensitivity assays. Identifying genetic mutations that are predictive of a response to treatment is more of a solid science. The goal would be to elucidate more mutations that can predict response to treatment and toxicity profiles.

Please note that ImpriMed does not look at chemosensitivity assays alone. Our AI models always use parameters from chemosensitivity assay, flow cytometry, PARR, patient signalment, disease stage, and bloodwork. We are trying to add genetic components into our AI models to further improve accuracy of predicting clinical outcomes.

I am unfamiliar with the avenue that ImpriMed uses to collect follow up data – perhaps for someone like me who is not in clinical practice, they could give us an overview and we can provide insight and ideas as to how to be most efficient at

collecting follow up data.

So far, we've been collecting patients' follow-up charts from clinics (based on the signed consent forms) 3 months after we provided our prediction reports.

Do we know the time frame that dogs progressed with the different mutations? Like how long did it take the dogs with the PSR1 to relapse? I would also like to get more information on dogs treated with other therapies than CHOP. For example, dogs who's Imprimed results were T cell lymphoma and should respond to a LOPP type protocol. How did those dogs do?

Yes, we can calculate the time frame but with such a small sample size, we can't make any claims about the exact time frame to progression with different mutations. We can only make general inferences at this point. That type of granular detail will have to wait for our next larger study.

Jaguar Health has partnered with healthcare communications agency TogoRun and animal health software company Ivee to create the *Take C.H.A.R.G.E.* (Canine Health And Registry Exchange) – a first-of-its-kind national canine cancer registry to provide the U.S. veterinary community and dog owners with valuable data to help guide canine cancer diagnosis and treatment.
Launched in May 2022, the Registry began with a retrospective review of de-identified and anonymous canine patient records from Ivee's secure, cloud-based platform. To date, nearly 36,000 canine medical records have been accessed and uploaded to the dashboard, with more than 830 cancer diagnoses confirmed. Veterinary clinics and pet owners are encouraged to submit canine cancer patient records. This can be done easily and at no cost, and all uploaded records are fully anonymized.

DATA CAPTURE
The Registry captures:
•State-by-state prevalence and incidence of cancer (by type)
•Treatment approaches and outcomes
•The impact of cancer and treatment side effects on dogs and pet owners, including chemotherapy-induced diarrhea, nausea, vomiting, fatigue, inappetence, etc.
•Demographics of dogs with cancer (breed, type, age, gender, location)
There are many moving parts to achieving a successful medical outcome in treating CID, and actively engaging with the pet owner is a critical part. Owner education will be available from Jaguar Animal Health.

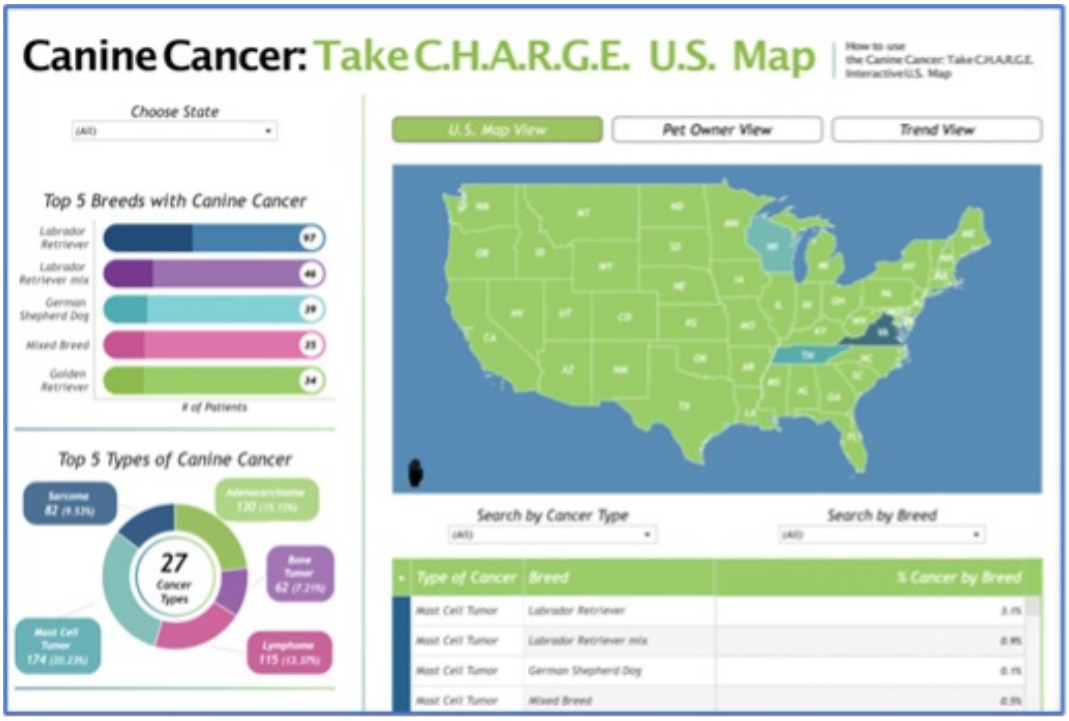
CANCER CODING SYSTEM
The *Take C.H.A.R.G.E.* Registry plans to pursue the adoption of a consistent canine cancer diagnostic coding system, supporting the goals of the National Institute of Health/National Cancer Institute Comparative Oncology Program.
In support of comparative oncology, the Registry intends to incorporate, and encourage veterinary clinics to adopt, coding practices that align with the recently

published Veterinary International Classification of Diseases for Oncology Canine Tumors First Edition, or Vet-IDC-O-canine1. Adoption of the Vet-IDC-O-canine1 coding system is intended to enable “apples to apples” comparisons of canine cancers in the United States and other countries.

SCIENTIFIC ADVISORY BOARD

The Registry is led by a Scientific Advisory Board (SAB) of leading veterinary oncologists from across the country. The SAB includes Co-chairs: Dr. Craig Clifford and Dr. Terry Fossum; and members: Dr. Sue Ettinger, Dr. Trina Hazah, Dr. Chad Johannes, Dr. Doug Thamm, Dr. David Vail, and Dr. Rachel Venable.

There will be more information on the registry in future Monograph editions.



Link to Registry website

Summary of Avmaquin

Glucoraphanin, a precursor of sulforaphane, is found in broccoli and other cruciferous plants in addition to myrosinase, a ß-thioglucosidase enzyme. Through crushing the plant tissues, such as chewing or chopping, the myrosinase acts on the glucoraphanin, converting it, through a hydrolysis reaction, into sulforaphane.

Once released within the body, Sulforaphane elevates cytoprotective enzymes. Sulforaphane's primary cytoprotective effect occurs through activating the nuclear factor erythroid-derived 2-like 2 (Nrf2) protein into triggering the production of Phase-2 detoxification enzymes, thereby reducing oxidative stress.
Oxidative stress is responsible for destroying large biomolecules, such as lipids, proteins, and DNA, leading to poor health outcomes throughout the body. Research on sulforaphane has shown it as the most cited natural product activator of Nrf2, which reduces oxidative stress.
Following a decade of research, Nutramax Laboratories developed Avmacol® and Avmacol® Extra Strength (with maitake mushroom extract), a stable source of the precursor ingredients necessary to help promote sulforaphane production in the body. The Avmacol® brand has been used extensively in sulforaphane human clinical trials. More recently, Nutramax Laboratories has launched Avmaquin™ to promote sulforaphane production in dogs.
Consuming broccoli from the market is typically insufficient and may not contain all the necessary nutrients due to multiple factors. Avmaquin™ provides a stable and consistent source of glucoraphanin and myrosinase precisely formulated for dogs. Every batch is tested. Tablets are tasty, reliable and convenient, dosing is one chewable tablet daily.
Studies in human cells and rats have shown that sulforaphane can potentially improve or support against instances of TCC. Although there have been no specific sulforaphane studies in dogs (though a study is now underway at NCSU), a study of Scottish Terriers demonstrated that consuming vegetables at least three times per week reduced bladder cell issues by at least 70%. However, research on healthy dogs showed that sulforaphane was related to a decrease in histone deacetylase activity.
In a study of dogs diagnosed with multicentric lymphoma, treatment with sulforaphane was associated with major changes in the proteome of neoplastic lymphocytes[27]. In other canine research, *in vitro,* and *in vivo* studies indicated modest protection against osteosarcoma and, when used with doxorubicin, provided a significant protective effect against cancer and the stress caused by doxorubicin.

Nutramax Laboratories Veterinary Sciences Inc is providing free samples of Avmaquin to Veterinary Oncologists. So far, over 40 Veterinary Oncology Hospitals have received samples. Several have already given the product to their clients. Over the next month or so Nutramax Laboratories Veterinary Sciences Inc will be reaching out to these Veterinary Oncologists to receive initial feedback on Avmaquin.
If anyone would like to request Avmaquin samples please send an email to the link below.

Denamerin update

Over the last year to year and half Nutramax Laboratories Veterinary Sciences Inc has been dealing with global supply chain issues for our SAMe based products, Denamarin. Nutramax Laboratories Veterinary Sciences Inc is happy to announce that **DENAMARIN IS BACK.**

Why is this important?
In June of 2011 a clinical trial on the use of Denamarin in combination with CCNU in dogs was published. Below is the link to the study.

Paper summary:

Background: Increases in liver enzymes occur in up to 86% of dogs receiving CCNU and can result in treatment delay or early discontinuation of treatment. Denamarin contains S-adenosylmethionine and silybin, both of which have been investigated as treatments for various liver diseases.
Results: Increased liver enzyme activity occurred in 84% of dogs receiving CCNU alone and in 68% of dogs on concurrent Denamarin. Dogs receiving CCNU alone had significantly greater increases in ALT, aspartate aminotransferase, alkaline phosphatase, and bilirubin and a significantly greater decrease in serum cholesterol concentrations than dogs receiving concurrent Denamarin. Dogs receiving CCNU alone were significantly more likely to have treatment delayed or discontinued because of increased ALT activity.
Conclusions: Increased liver enzyme activity occurs commonly in dogs receiving CCNU chemotherapy. These results support the use of concurrent Denamarin to minimize increased liver enzyme activity in dogs receiving CCNU chemotherapy. Denamarin treatment also increases the likelihood of dogs completing a prescribed

CCNU course.

Currently there are three forms of Denamarin available to veterinarians:
1. Denamarin Advanced chewable tablet or hard tablet: Different SAMe salt than the original Denamarin, Increase bioavailability so pet owner can give less than the original Denamarin
2. Denamarin hard tablet: 30 count, blue tablet in a blister pack. This is the product that veterinarians have trusted and used year
3. "NEW" Denamarin BEIGE hard tablet: 30 count bottle, Same price and dose as the original Denamarin blue hard tablet, stable in the bottle presentation

If anyone has any questions on Denamarin please contact Tom Murrell (tmurrell@nutramaxlabs.com).

Thoughts on the presentation:
I very much like that the Avmaquin has significantly more data behind it than many supplements purported to reduce the risk of /treat cancer. I'm also thrilled to hear that a study is ongoing at NCSU and am extremely interested in the noted histone deacetylase activity - it would be really interesting to hear more about that mechanism and potential implications for treatment.

A number of studies have evaluated sulforaphane on HDAC activity and are still trying to understand the mechanism. To date only one study in healthy dogs evaluated HDAC activity:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6236138/

I agree that there is more data with Avmaquin and feel that it could be a useful addition in chemoprevention and treatment of cancer. It would be exciting if it can be used to prevent cardiomyopathy from doxorubicin.

This interaction is a recent area of interest in human clinical trials evaluating sulforaphane. A recent review describes some of the interest: https://www.frontiersin.org/articles/10.3389/fphar.2020.00567/full. Our human product Avmacol is currently being studied for effects on doxorubicin-associated cardiac dysfunction in patients with breast cancer (please see clinicaltrials.gov for a list of current and completed trials with Avmacol). Research has shown that use of sulforaphane supports against cardiac toxicity in patients receiving doxorubicin and could potentially enhance the effects of oncology management. We would consider support of such evaluations in dogs.

I reach for Nutramax products based on data and reputation. Loved the breakdown on products – send this to everyone! Pet owners love holistic/supplement options.

Every batch is tested- This is very important to me as there are so many supplements on the market that are not tested or controlled in any way. This is something I tell clients to look for- made by a company they know and who TESTS their product

Questions (concerns and clarification)
Will there be a potential role for utilizing this as a broad spectrum supplementation for cancer patients or will the focus be on TCC, LSA and potentially as an early preventative supplementation for certain breeds? As I have seen nausea with this supplement that resolves with a holiday and a smaller dose can the company comment on the potential impact on efficacy?

In human literature, sulforaphane has been studied *in vitro* and *in vivo* for a variety of conditions. We will continue to evaluate other opportunities for Avmaquin in veterinary patients.
It is possible some dogs, as with people, may have more GI sensitivity when taking these ingredients. We don't have any data available at doses other than the recommended administration on the packaging.

I am assuming that the Denamarin that is a blue tablet and a beige tablet is the same product just in a different packaging?

Correct, the actual coating color on the hard tablets is different. The blue and beige hard tablet products have the same bioavailability (studies have been completed). Denamarin is now available in easy to open bottles.

What is the concentration of sulforaphane in Avmaquin?

Avmaquin does not contain sulforaphane, but rather the necessary ingredients (glucoraphanin and active myrosinase enzyme) to promote sulforaphane production in the body. The concentrations of these are not provided.

For the Denamarin Advanced- can it be given with food as its more orally bioavailable?

Denamarin Advanced should be given on an empty stomach, but because of the higher bioavailability may be administered with a small amount of food/treat.

Any Experiences with this or similar offerings

I use Denamarin religiously and love it, super glad to hear the supply issues are resolved!

I also use denamarin religiously and am very happy to hear that the issues are resolved. I have also started to utilize Avmaquin in all of my TCC patients. It is too early to tell yet the benefit, so far I find it is well tolerated, main issue I have seen and it has been in small dogs is nausea. I have given the patients drug holidays and then started on lower dose.

I also use denamarin religiously as well. Even in my own dog with liver enzyme elevations – chronic hepatopathy and pancreatitis – moved to the chewable and much more tolerable. I tell clients to stick with this product despite cost higher than OTC generics/human formulations.
I always have dogs on denamarin who are also getting lomustine.

I've started recommending Avmaquin for all TCC patients but I have no way to determine its efficacy at this time. I've only had one client say that their pet does not like the taste and spits them out. I give the Avmaquin pamphlet to my owners for reading

Thoughts for the future

I don't know if this is possible, but I'd be really interested to hear if Deborah Knapp's group at Purdue has an opinion on this product?
(Tariq – I have a meeting with Purdue in a couple of weeks – I will ask them!! :-)

I am interested in seeing what the recommended dosing and schedule for cardio protection from doxorubicin will be. This would be great for dogs that have pre-existing heart disease that you still really need doxorubicin for i.e., Splenic hemangiosarcoma.

I feel that the work being done on chemoprevention is exciting and would like to see more regarding other chemo preventives as well as nutritional supplements that can help with toxicity.

The science that has been done with the Avmaquin makes it easier to recommend it as we know the mechanism of action which is something that we do not know with many of the other supplements.

The doxorubicin in vitro study (https://pubmed.ncbi.nlm.nih.gov/27045198) mentioned in the summary found lower concentrations of sulforaphane lead to pro-proliferative and protective tumor effects against doxorubicin and the researchers then cautioned against using sulforaphane in dogs with chemotherapy until further studies are performed. So is the supplement recommended to give with chemotherapy, or is this supplement better to help prevent cancer, or for pets with cancer who are not getting treatment with chemotherapy?

In human literature, sulforaphane has been studied in combination with chemotherapeutics *in vivo*. Combinations have not been studied *in vivo* in dogs to date.

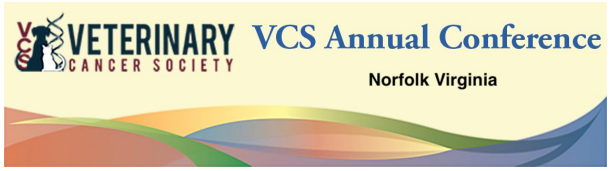
Like the Denamarin/ CCNU study with ALT, is there is any biomarker or value we can evaluate clinically to determine response with Avmaquin in patients? Does it

have any affect on % mutation of BRAF in urine?

Based pilot study data, we anticipate changes in BRAF mutation rate, but the data from our larger clinical trial is not available for sharing at this time.

Email me if you would like some free samples for your hospital to trial

Link to Denamarin abstract



"Please provide your thoughts on VCS and anything you found particularly interesting":

The focus on liquid biopsy was interesting and definitely gave them a much wider audience then I think they've had before; I had not heard a lot of that data before. After the epigenetics talk I'm very interested in using vorinostat for cutaneous lymphoma! The resident abstracts seemed more heavily weighted towards benchtop over clinical research. The upcoming research from Cheryl London and Heather Robles in treatment of lymphoma was super interesting and I can't wait to see what their next trials are going to show!

I found the MCT panel really interesting and helpful. I wish they would do more of these. In particular I feel the discussion of use of the prognostic panel was 1) a great review and 2) helped to define use and make me feel better that I recommend it more than many people I have worked with over the years. I also liked the discussion on breaking down the panel and if you had to pick only one part of it which would you choose. My take away was if it is a low grade concerning utilize Ki67 vs. If high grade (ie we know its bad) then ckit status to help determine Palladia vs. Vinblastine. I hope I remembered this part of the discussion correctly. Also good to know the entire college thinks kit pattern is useless.
I found the idea of using the liquid biopsy for tracking lymphoma remission interesting as well as utilizing it for marginal/narrow excisions to help determine if there is truly residual disease present to warrant more aggressive local control.
I second the London research for immunotherapy for lymphomas I heard a lot of optimistic talk and excitement on this presentation. I also second the use of vorinostat for the cutaneous LSA.

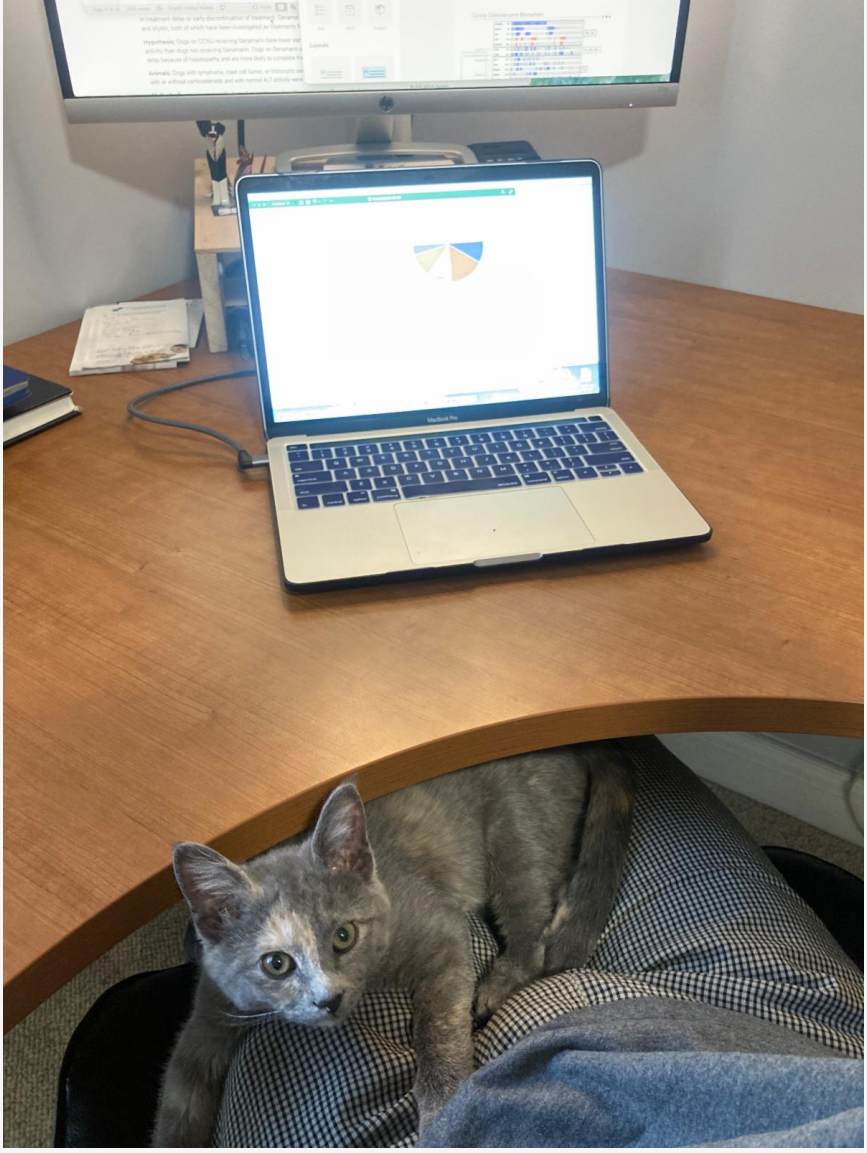
I was excited to be at VCS since it has been at least 4-5 years since I have gone. It was nice to see that there were so many vendors at VCS and so many companies that were sponsors. I am actually glad to see that there were so many technicians that were there since we depend on them.
I think that the roundtable presentations were very enlightening as it gave me a chance to see what leaders in the field are researching and what they are actually doing with their cases. Despite the technology that is being developed, it did not seem that the way that they practiced at this time was significantly different from what I have been doing.

Overall I have always found that VCS tends to follow themes – this year's

highlighted cancer diagnostics – early detection, predicting response to therapy and monitoring. It is great to see so many companies making significant progress in this arena. I was pleased that the overall majority recognize that the place and use of these diagnostics are still finding their way into clinical practice. I think most oncologists will be proactive in taking the time to understand and help find the best use of these tests – hopefully teaching the referral clinics to find a responsible use for them. I hope that we do not have another ten years of "the mast cell tumor" panel use where primary care veterinarians run panels that cost several hundred dollars and may be useless or not necessary in many cases. This is where oncologists (along with these companies) should lead the charge on education. We also need to show the benefits of early diagnosis/detection of relapse and response – recognizing it is early, patient benefit and outcome needs to be identified vs just using a "really cool" test. Good to see majority of companies are recognizing this too.
Format of VCS – large kudos to the MCT panel! It was built as just several colleagues having a discussion and highlighted many controversies that we all want to hear how colleagues resolve. The format of specific focus sessions has improved the VCS content markedly.
Through the grapevine (from "seasoned" colleagues that have attended VCS for 20 years) the feeling is that the format has improved but become incredibly commercialized with one company after another doing the bidding prior to a session. I come from both sides in that this may be the only opportunity in a year for industry to provide significant digestible information to specialists and it provides support for the conference to maintain quality and attempt to keep costs for attendees lower.

I found the pre- conference workshop on integrative medicine really well done and enjoyed that they discussed interactions with chemotherapy and also patients with other systemic illness. We get so many questions on this and I at least am lacking knowledge in this area of medicine.
Cheryl London's work is absolutely fabulous but it will be years until we will have something clinical to work with.
I enjoyed all the information on small molecule inhibitors with the toceranib and imatinib target receptor circle plots. I'm using imatinib in quite a few MCTs when they are resistant to Palladia. I would love to have mastinib back as another option for cases.
The mast cell tumor panel discussion was great and having a pathologist involved to discuss the IHC/ PARR options was very helpful. It's just nice to see how everyone is approaching these cases.

I received a lot of "help" writing this edition



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