Harnessing the Integrated Canine Data Commons (ICDC) and the PRECINCT Canine Immunotherapy Trials Network to Advance Discoveries in Cancer Genomics

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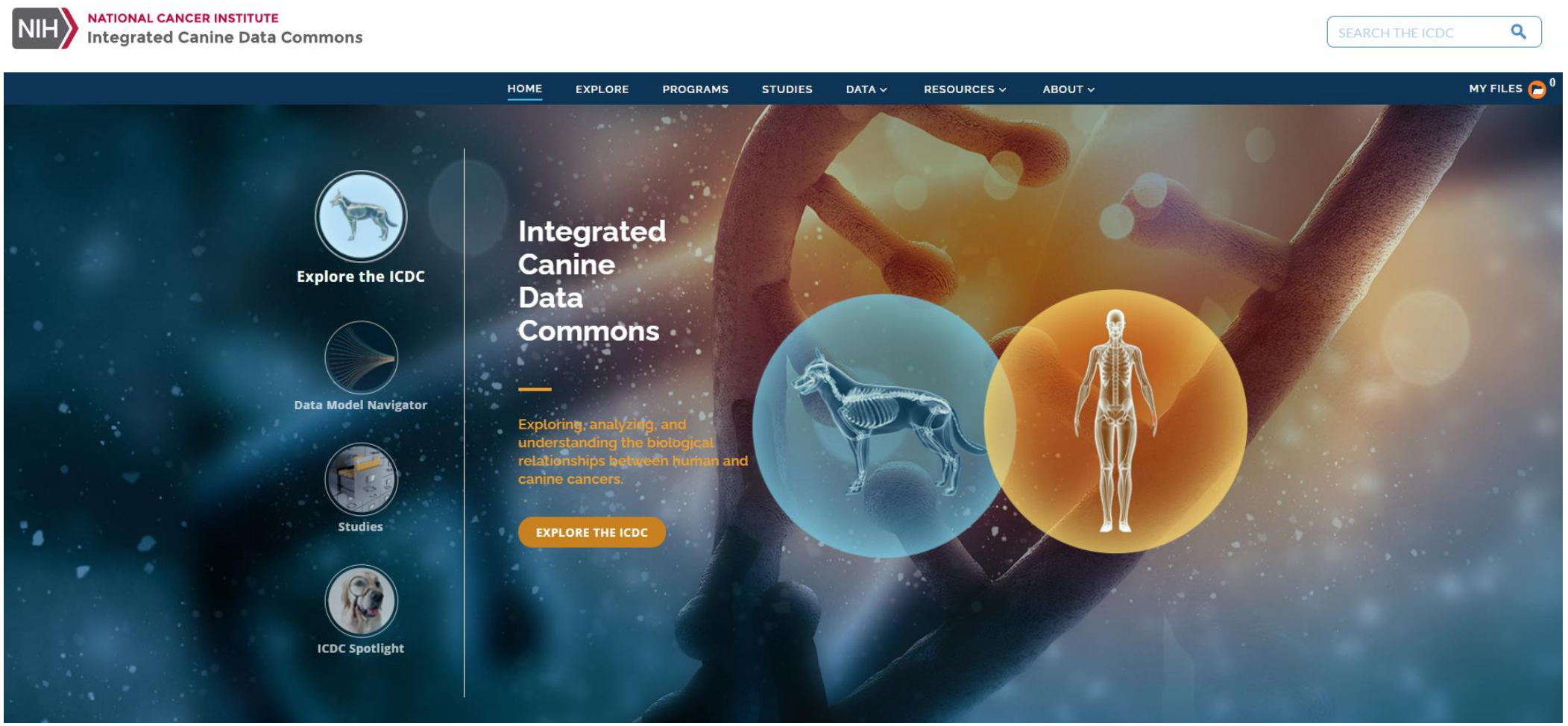
NCI's Integrated Canine Data Commons: ICDC



Comparative Oncology

Comparative oncology: the study of naturally-occurring cancer in animals aimed at learning new information to better understand and manage cancer in humans.

Similarities and differences between species are informative.

Most of our work involves pet dogs.

Naturally-occurring models complement experimental models.

Research Applications in Comparative Oncology

1. Treatment trials and studies to improve cancer management

2. Cancer prevention

- Causes of cancer

- Early detection and intervention

3. Cancer biology

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Investigation of Novel Topoisomerase 1 Inhibitors

Mark Cushman Mike Childress “Atticus”

Yves Pommier

NCI - COTC

Data in ICDC: COTC0078, Preclinical comparison of three indenoisoquinoline candidates in tumor-bearing dogs; Accession ID 000005

Published OnlineFirst July 30, 2018; DOI: 10.1158/1078-0432.CCR-18-1498

Research Article

Clinical Cancer Research

NCI Comparative Oncology Program Testing of Non-Camptothecin Indenoisoquinoline Topoisomerase I Inhibitors in Naturally Occurring Canine Lymphoma

Jenna H. Burton[1], Christina Mazcko[2], Amy LeBlanc[2], Joseph M. Covey[3], Jiuping Ji[4], Robert J. Kinders[4], Ralph E. Parchment[4], Chand Khanna[2], Melissa Paoloni[2], Sue Lana[5], Kristen Weishaar[5], Cheryl London[6], William Kisseberth[6], Erika Krick[7], David Vail[8], Michael Childress[9], Jeffrey N. Bryan[10], Lisa Barber[11], E.J. Ehrhart[5], Michael Kent[1], Timothy Fan[12], Kelvin Kow[13], Nicole Northup[14], Heather Wilson-Robles[15], Joseph Tomaszewski[3], Julianne L. Holleran[16], Miguel Muzzio[17], Julie Eiseman[16], Jan H. Beumer[16], James H. Doroshow[3,18], and Yves Pommier[18]

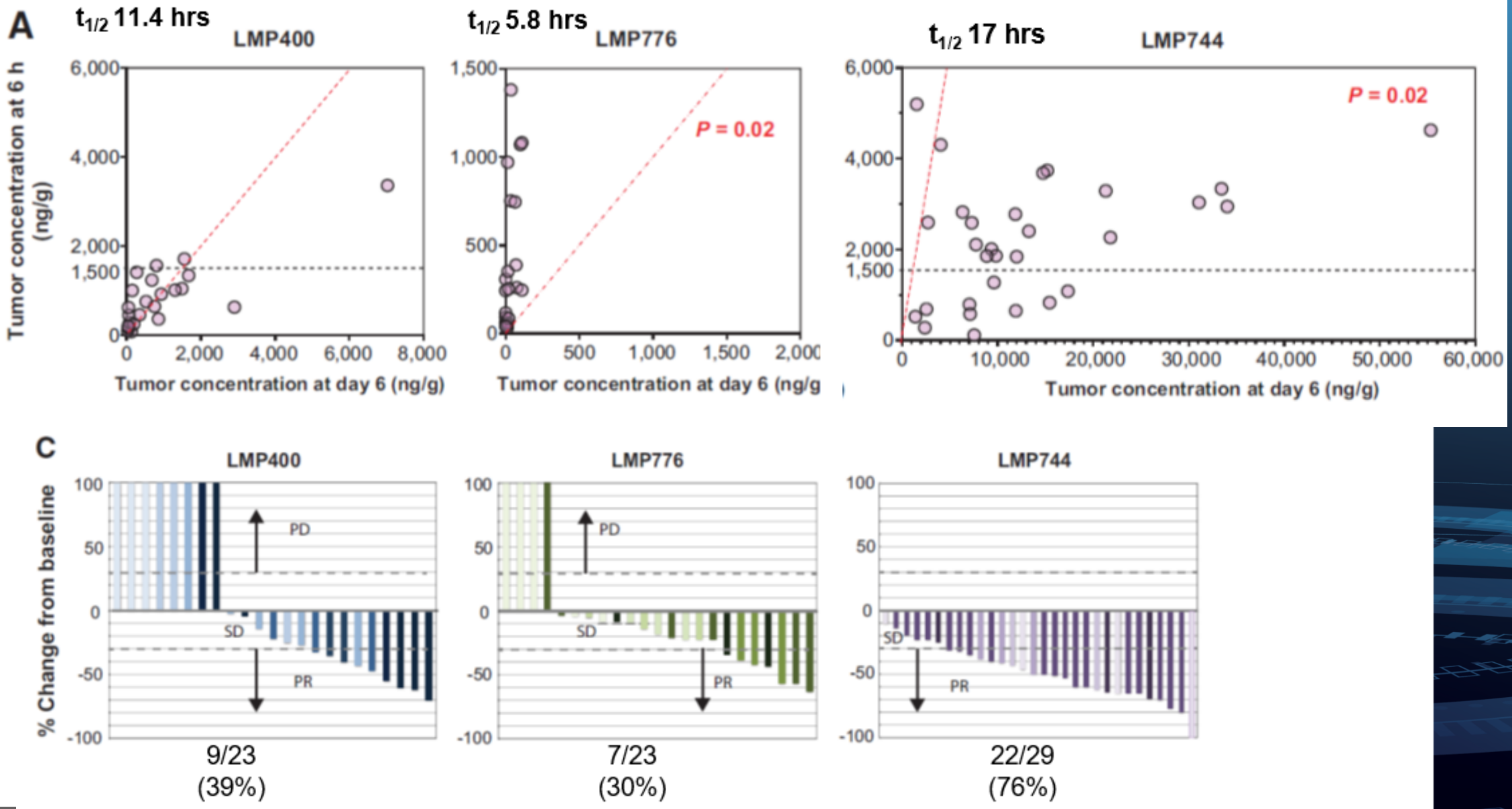
Novel Topoisomerase 1 Inhibitors – Dog Study

- Indenoisoquinolines
  - Non-camptothecin TOP1 inhibitors
  - Improved bioavailability
  - Not subject to ABC transporter efflux

- Three drugs tested in dogs
  - LMP400 (also in human trials)
  - LMP776 (also in human trials)
  - LMP744

- Goals: determine MTD, PK/PD, and anticancer activity in dogs with lymphoma

Novel Topoisomerase 1 Inhibitors – Dog Study



Burton et al., Clin Cancer Res 2018

LMP744 Moved Into Human Trial: NCT03030417

Meeting Abstract: 2023 ASCO Annual Meeting

Phase 1 study of indenoisoquinoline LMP744 in adults with relapsed solid tumors and lymphomas.

Authors: Brian Ko, Alice P. Chen, Shivaani Kummar, Murielle Hogu, Larry V. Rubinstein, Naoko Takebe, Richard Piekarz, ... SHOW ALL ..., and Geraldine Helen O'Sullivan Coyne | AUTHORS INFO & AFFILIATIONS

Key Findings:

Favorable PK profile

While antitumor activity limited, patients had received a median of 5 prior therapies

Prolonged cancer stabilization in 4 patients with colorectal cancer with prior progression on another TOP1 inhibitor (irinotecan)

Research Applications in Comparative Oncology

1. Treatment trials and studies to improve cancer management

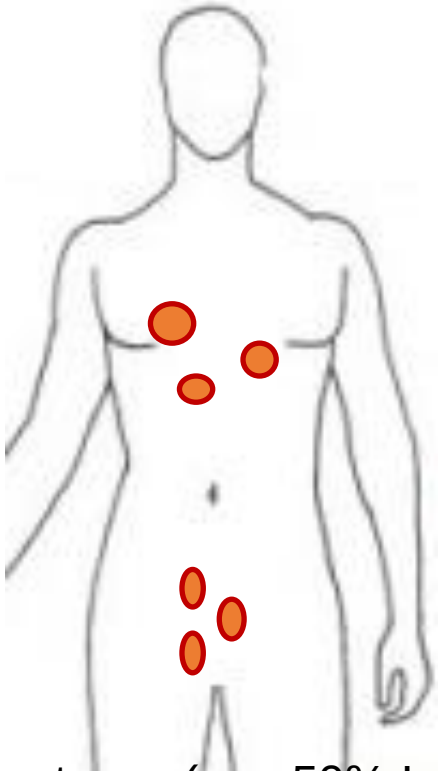
2. Cancer prevention – Examples in invasive urothelial carcinoma

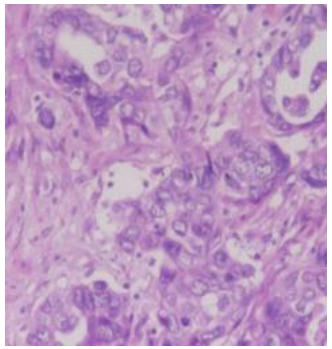
- Causes of cancer
- Early detection and intervention

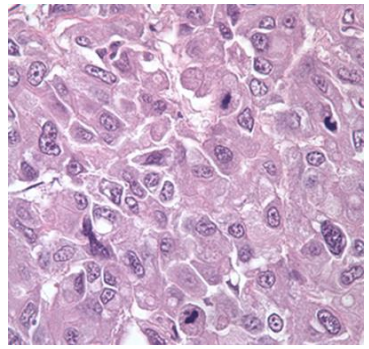
3. Cancer biology

Canine Invasive Urothelial Carcinoma: Highly-Relevant Naturally-Occurring Model of Human Muscle Invasive Bladder Cancer

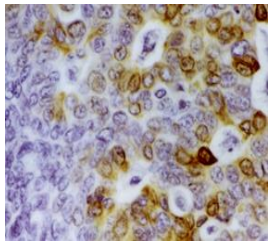
Age of Onset and Symptoms



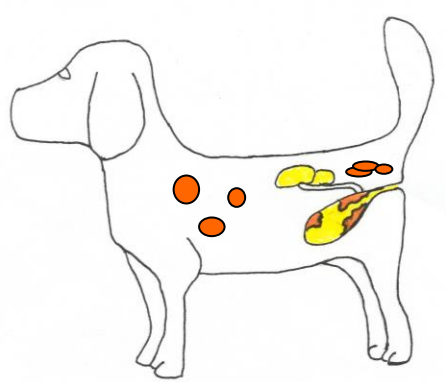




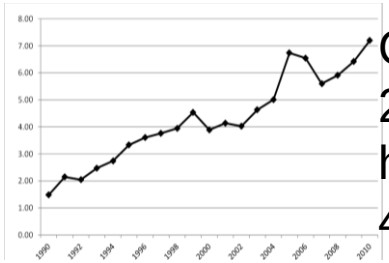
Cellular Features and Pathology
High Grade Invasive



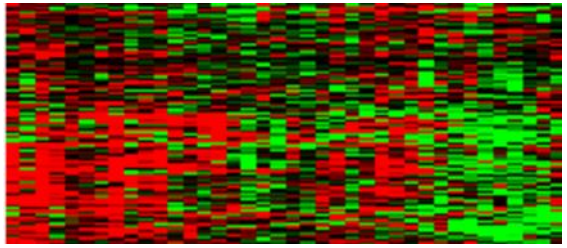
Heterogeneity



Sites and Frequency of Metastases (e.g. 50% Lung)



Case Numbers:
25-30,000 humans
40-60,000 dogs



Molecular Subtypes

Treatment Response

Knapp et al., Front Oncol 2020,
Wong et al., Genome Biol 2023

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Reducing the Risk of Bladder Cancer

Humans

Dogs

Knapp et al., ILAR 2014; Smith et al., Vet Comp Onc 2022; Braman et al., Vet Comp Onc 2024

Risk Factors for Bladder Cancer – Additional Factor in Dogs - Exposure to Marsh

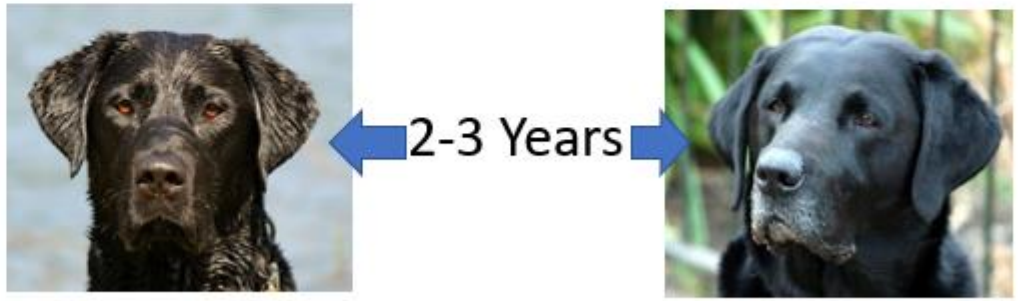
Higher risk in Scottish Terriers living within a mile of a marsh,
OR 21.2, 95% CI 3.6-123.7; P=0.001

Knapp et al., Vet J 2024

Early Detection and Early Intervention Research

Unique opportunities in bladder cancer prevention research in dogs

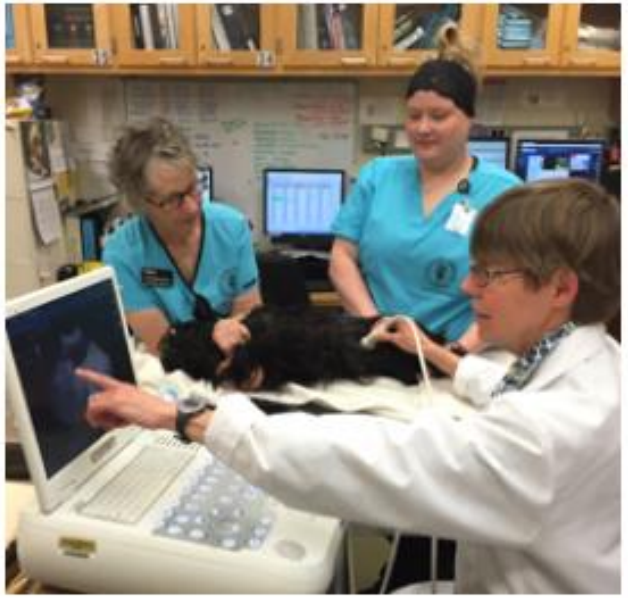
Breed-associated risk



Compressed life span in dogs

Knapp et al., ILAR J 2014

Early Detection and Early Intervention of Bladder Cancer in Scottish Terriers



- 120 Scottish Terriers, ≥ 6 yrs old
- Screen: 6-month intervals X 3 yrs, US + UA
- Cystoscopy and biopsy if positive screen test(s)
- Deracoxib intervention trial

Dhawan et al., Front Oncol 2022

Key Findings Included:

1. Cancer can be found early through screening: biopsy confirmed cancer in 40 dogs with no clinical signs.

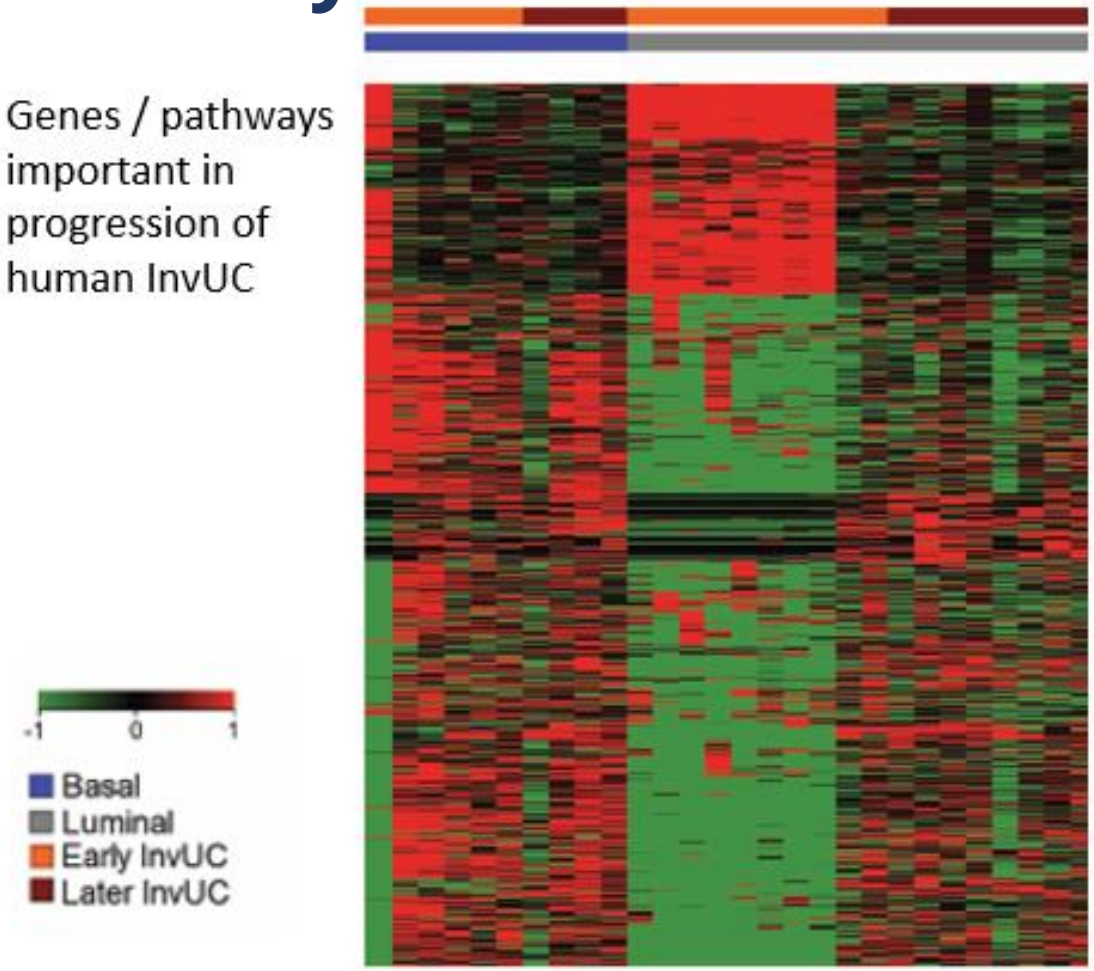
2. Early treatment makes a difference: 42% remission rate and median PFI 304 days with conservative oral therapy.

3. Living in a household with cigarette smokers or detection of cotinine in the dog's urine significantly increased cancer risk.

4. Marked differences in genes and pathways between cancer detected early and late.

Knapp et al., Vet J 2024

Differences In Genes and Pathways Between Cancer Detected Early and Late



RNA-seq Data Submitted to **ICDC, UBC03**
Comparison Data in **ICDC UBC02**, Accession number 000005

Dhawan et al., Front Oncol 2022, Sommer et al., Bladder Cancer 2021

NCI Support for Comparative Oncology Research

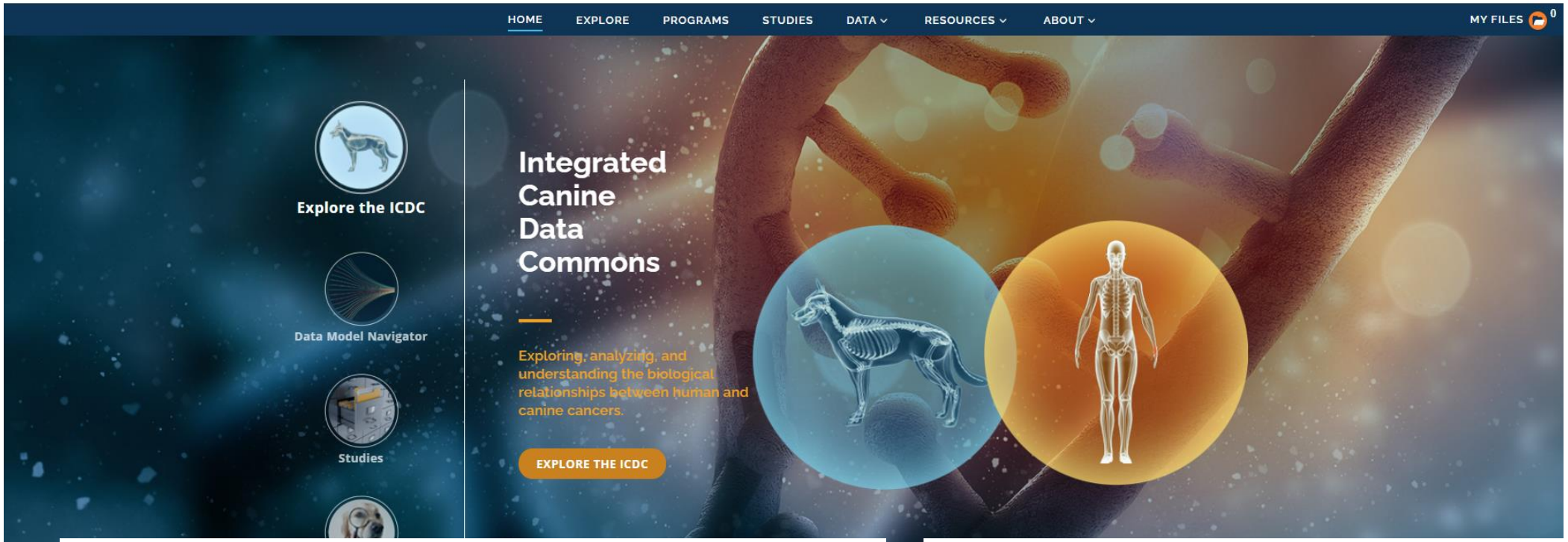
1. Intramural research including the NCI's Comparative Oncology Program and the COTC

2. Investigator-initiated research across grant programs and supplement grants

3. Integrated Canine Data Commons (ICDC)

4. PRECINCT

ICDC



Veterinary and Comparative Oncology

REVIEW | Open Access

Leading the pack: Best practices in comparative canine cancer genomics to inform human oncology

Cheryl A. London, Heather Gardner, Shaying Zhao, Deborah W. Knapp, Sagar M. Utturkar, Dawn L. Duval, Melissa R. Chambers, Elaine Ostrander, Jeffrey M. Trent, Gina Kuffel

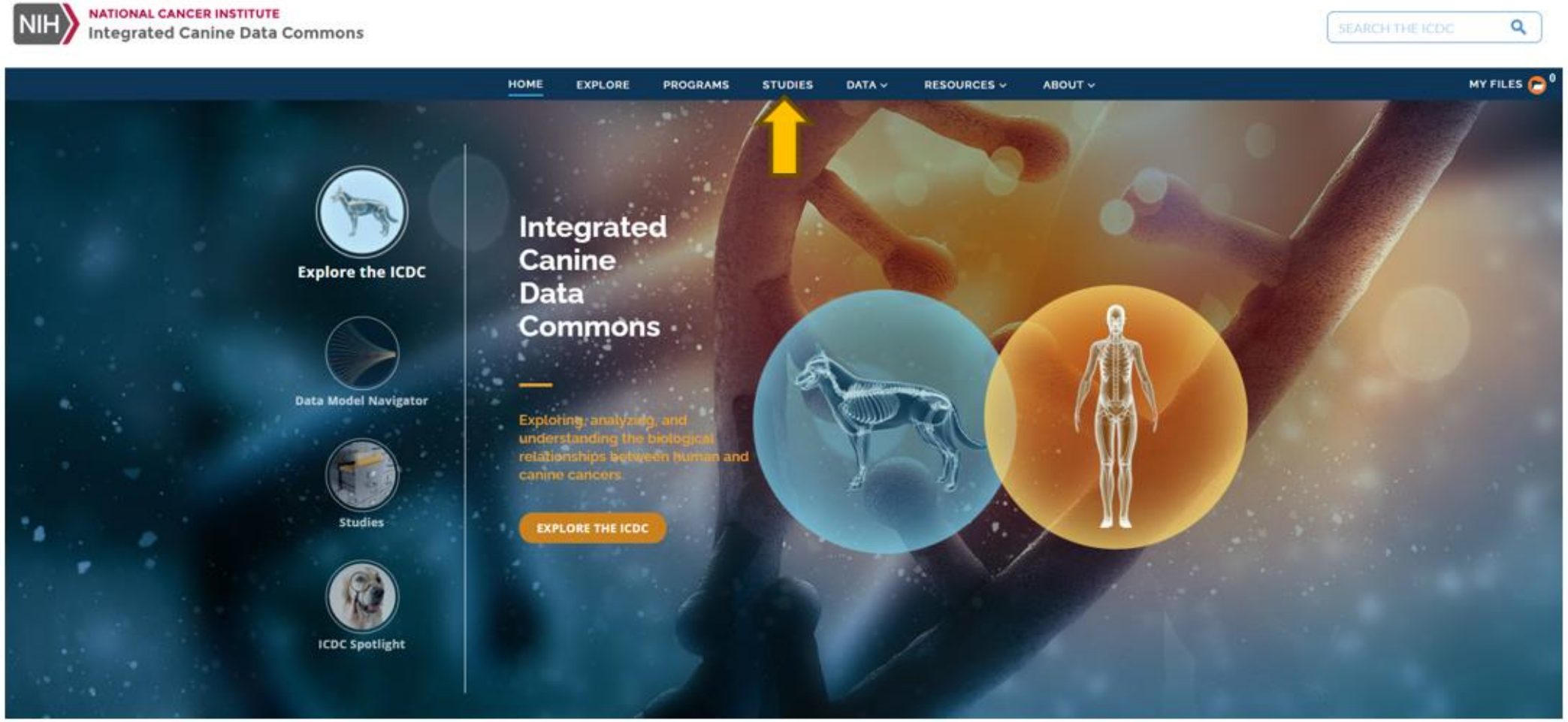
First published: 01 October 2023 | https://doi.org/10.1111/vco.12935

CANCER RESEARCH | REVIEW

NCI Cancer Research Data Commons: Resources to Share Key Cancer Data

Zhining Wang[1], Tanja M. Davidsen[1], Gina R. Kuffel[2], KanakaDurga Addepalli[1], Amanda Bell[2], Esmeralda Casas-Silva[1], Hayley Dingerdissen[2], Keyvan Farahani[1], Andrey Fedorov[3], Sharon Gaheen[2], Robert L. Grossman[4], Ron Kikinis[3], Erika Kim[1], John Otridge[2], Todd Pihl[2], Melissa Porter[5], Henry Rodriguez[6], Louis M. Staudt[5], Ratna R. Thangudu[7], Sudha Venkatachari[2], Jean Claude Zenklusen[5], Xu Zhang[6], The CRDC Program, Jill S. Barnholtz-Sloan[1,8], and Anthony R. Kerlavage[1]

Cancer Defined by Organ and Cancer Defined by Mutation Profile



ICDC – Cancer Defined by Organ, e.g. Invasive Urinary Bladder Cancer

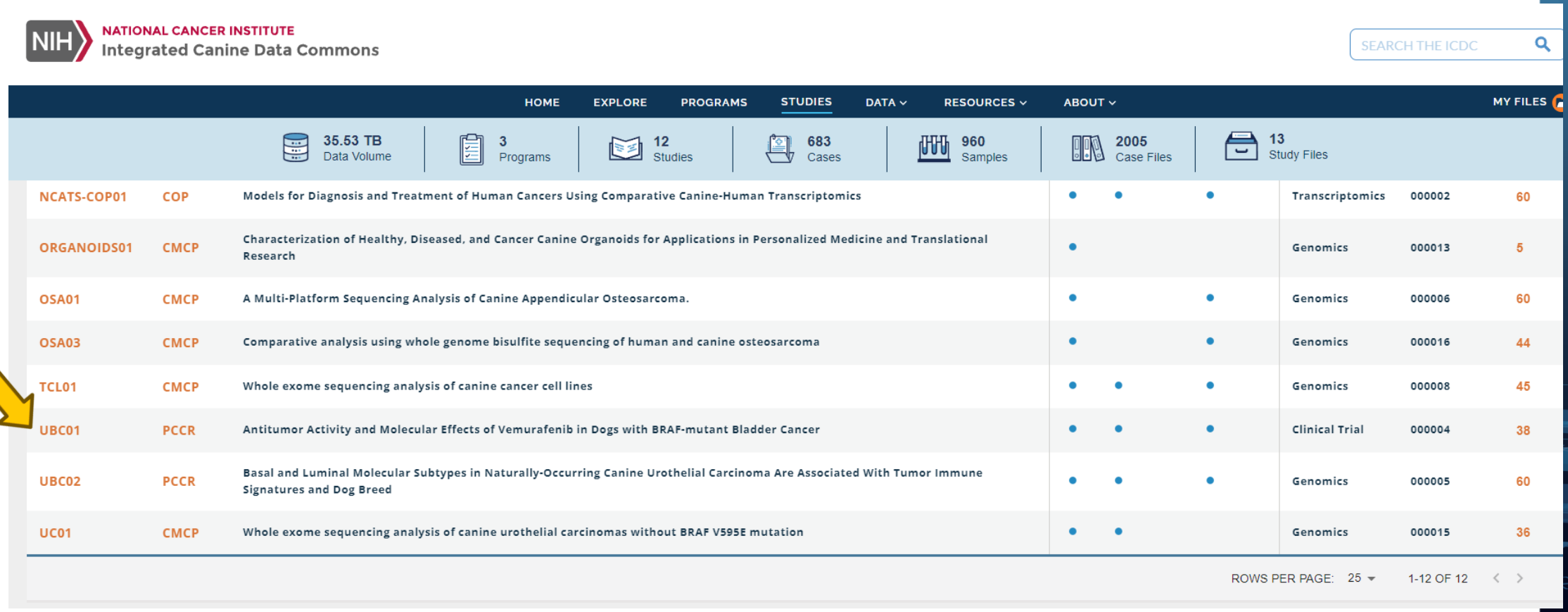
Study Code	Program	Study Name	Data Availability	Study Type	Accession ID	Cases
ORGANOIDS01	CMCP	Characterization of Healthy, Diseased, and Cancer Canine Organoids for Applications in Personalized Medicine and Translational Research	●	Genomics	000013	5
OSA01	CMCP	A Multi-Platform Sequencing Analysis of Canine Appendicular Osteosarcoma.	● ●	Genomics	000006	60
OSA03	CMCP	Comparative analysis using whole genome bisulfite sequencing of human and canine osteosarcoma	● ●	Genomics	000016	44
TCL01	CMCP	Whole exome sequencing analysis of canine cancer cell lines	● ● ●	Genomics	000008	45
UBC01	PCCR	Antitumor Activity and Molecular Effects of Vemurafenib in Dogs with BRAF-mutant Bladder Cancer	● ● ●	Clinical Trial	000004	38
UBC02	PCCR	Basal and Luminal Molecular Subtypes in Naturally-Occurring Canine Urothelial Carcinoma Are Associated With Tumor Immune Signatures and Dog Breed	● ● ●	Genomics	000005	60
UC01	CMCP	Whole exome sequencing analysis of canine urothelial carcinomas without BRAF V595E mutation	● ●	Genomics	000015	36

Mining UBC Data in ICDC

Example: cTULIP: application of a human-based RNA-seq primary tumor classification tool for cross-species primary tumor classification in canine. Long J, et al. Front Oncol 2023;13:1216892. PMID: 37546395

Example: Unbiased discovery of cancer pathways and therapeutics using Pathway Ensemble Tool and Benchmark. Wang L, et al. Nat Commun 2024;15:7288. PMID: 39179644

ICDC – Cancer Defined by Gene Signature, e.g. *BRAF^{V595E}* Associated Cancer

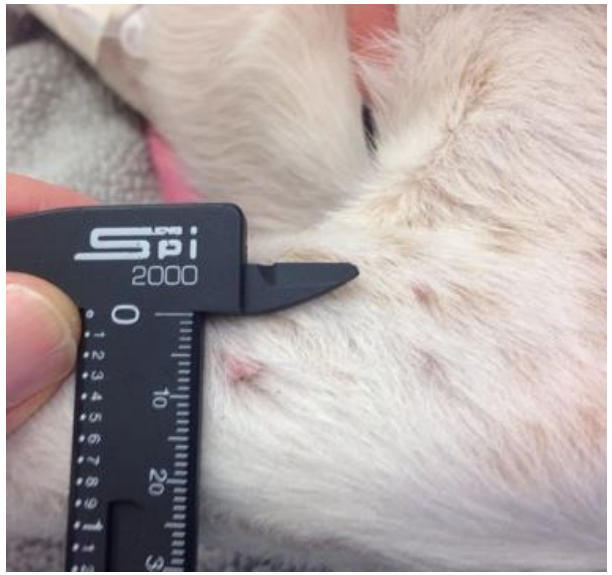


UBC01 – Antitumor Activity and Molecular Effects of Vemurafenib in Dogs with *BRAF*-mutant Bladder Cancer

Good initial antitumor activity (38% remission rate) followed by acquired resistance mimicked that in humans

Defined pharmacokinetic and pharmacodynamic effects

Genomic effects in responding and resistant tumors



ICDC UBC01

Rossman et al., Mol Cancer Ther 2021

Gene Expression Changes With Vemurafenib (Vem)

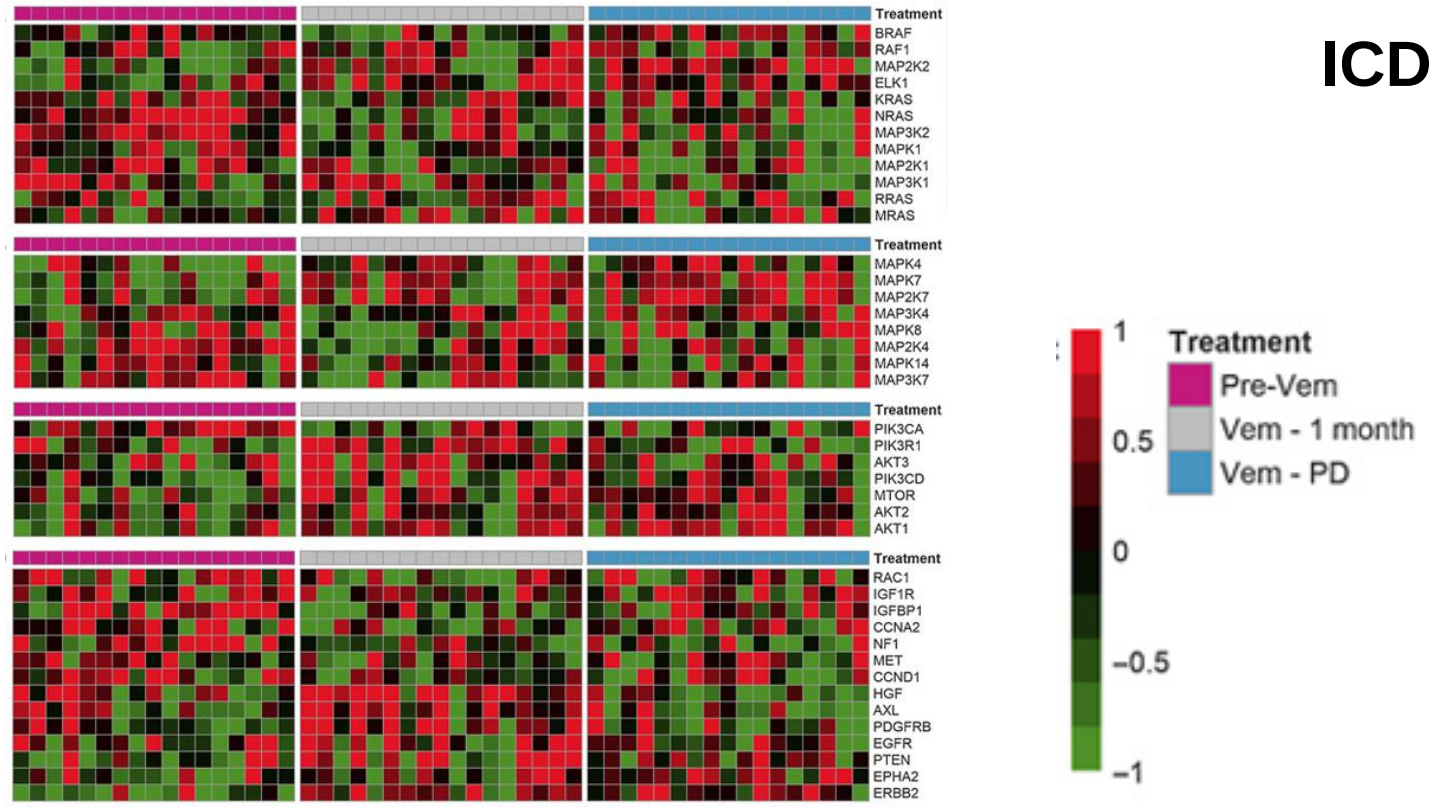
ICDC UBC01

Classical MAPK

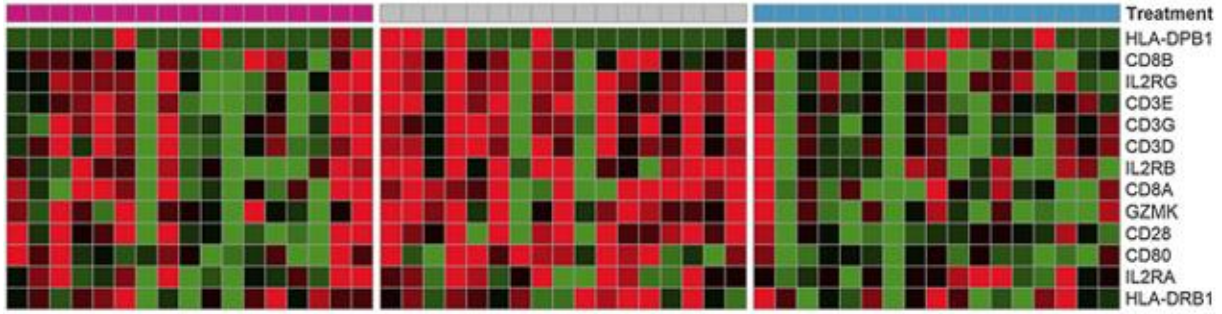
Stress-JNK

PI3K/AKT/mTOR

Genes involved in Vem resistance



Genes involved in enhanced immune response



Rossman et al., Mol Cancer Ther 2021

UBC01 – Data in ICDC

ICDC UBC01

STUDY FILES PUBLICATIONS

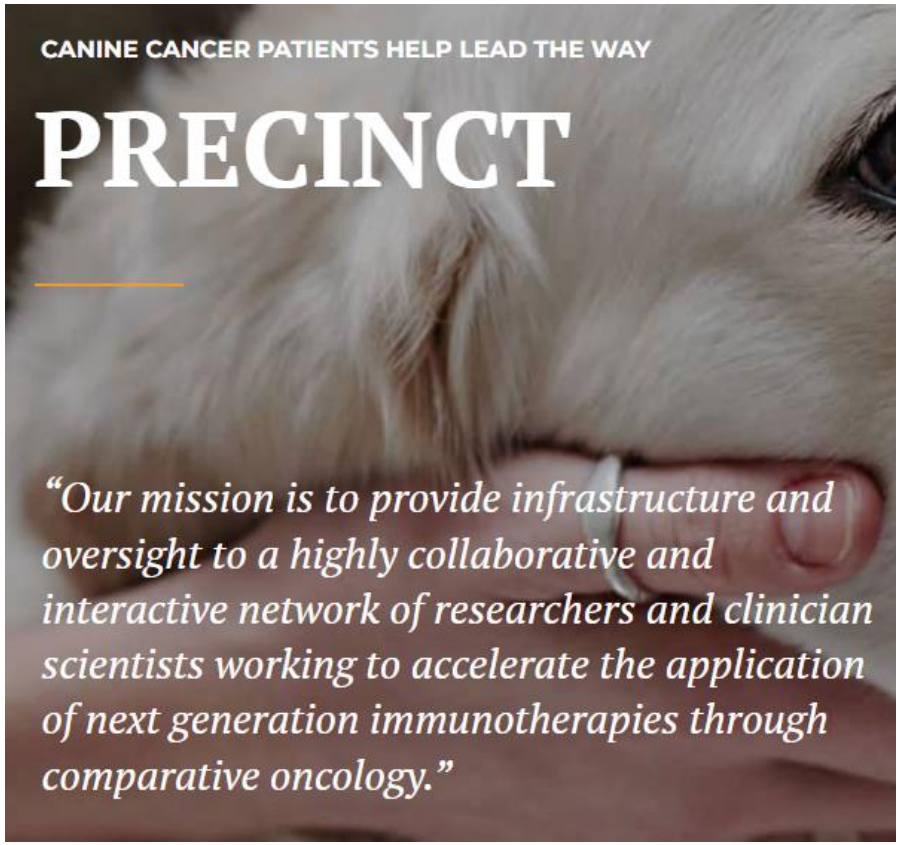
directly associated with it:

	File Type	Association	Description
	Supplemental Data File	study	Luminal and basal molecular subtypes
	Supplemental Data File	study	Vemurafenib pharmacokinetics data
	Study Protocol	study	Background, methods, and key findings
sx	Supplemental Data File	study	Treatment response, survival, and necropsy data

Please use ICDC data and add data to the Commons!

PRECINCT – U01 Grant Supported Canine Immunotherapy Trials and Coordinating Center

https://www.precinctnetwork.org



PRE-medical Cancer Immunotherapy Network
PRECINCT Canine Trials

Grants awarded in 2017 and 2022, 10 studies supported to date

Looking to the Future of ICDC

Add more studies and data to ICDC

Model validation → use of the models

Motivate the scientific community to make more use of the data

- Conduct and publicize high-impact studies
- Reach out to disease-focused groups and others
- Consider incentivizing use

Thank You For Your Interest!

Werling Comparative Oncology Research Center
The “Purdue Team” in Comparative Oncology

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