ASU Complex Adaptive Systems Initiative
Arizona State University

The Evolving Landscape for Precision Health and One Health: New Opportunities in Human and Veterinary Medicine

Dr. George Poste
Regents Professor and Del E. Webb Chair in Health Innovation
Chief Scientist, Complex Adaptive Systems Initiative,
Arizona State University
george.poste@asu.edu

Keynote Presentation
Comparative Medicine Symposium
Arizona State University
30 November 2023

Slides Available at: **https://casi.asu.edu/presentations/**

Disclosures

EXELIXIS®	Board Member
CARIS® LIFE SCIENCES	Board Member
MEDISIX THERAPEUTICS	Board Member
BIPARTISAN COMMISSION ON BIODEFENSE	Board Member
UNIVERSITY OF MICHIGAN	Scientific Advisory Board
VIR	Scientific Advisory Board

Disclosures

Board Member

Board Member

No GAI Platforms Were Used in Content Selection, Design, Assembly and Formatting This Presentation

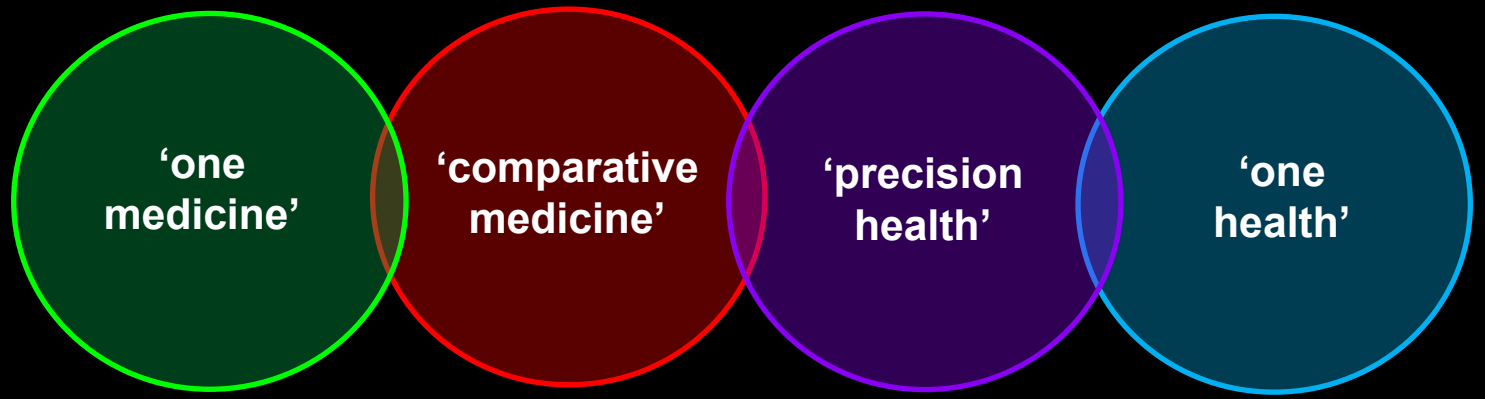
Scientific Advisory Board

Scientific Advisory Board

Presentation Outline

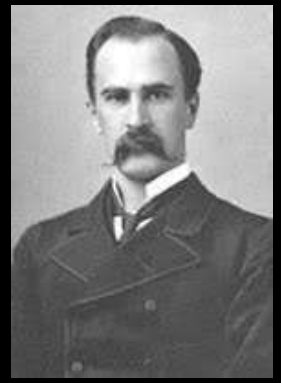
- the evolution of the relationships between human and veterinary medicine
- a new era of precision health
  - major opportunities for veterinary medicine from diffusion of new technologies from human medicine
  - imperative to reduce the unsustainable cost of high failure rates of new candidate human therapeutics in clinical trials
  - need for new animal models for preclinical testing of new human therapeutics that more accurately reflect the causal etiologies of the targeted human diseases
  - growing recognition of the appeal of many natural canine diseases as more predictive preclinical models of major human diseases
- one health
  - complex inter-dependencies of human and animal health and global ecosystems
  - an underinvested core component of global biosecurity

The Historical Evolution of Relationships Between Human and Veterinary Medicine (1850-present)



The One Medicine: One Health Concept
A Long Intellectual Pedigree

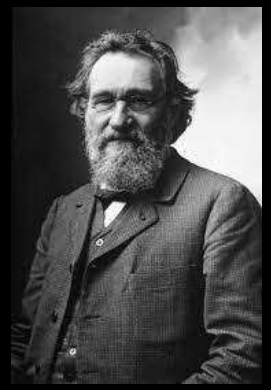
Rudolf Virchow
introduction of term zoonosis:
T.spiralis
1850



Sir William Osler
concepts in
comparative medicine
1870s

Robert Koch
anthrax, cholera, TB,
trypanosomisasis
1870-80s
Nobel Prize 1905

Sir Ronald Ross
anophelian mosquitos
and malaria transmission
1897
Nobel Prize



Elie Metchnikoff
comparative immunology
and host defense
1890s
Nobel Prize 1908

Paul Ehrlich
antimicrobial
chemotherapy
Noble Prize
1908

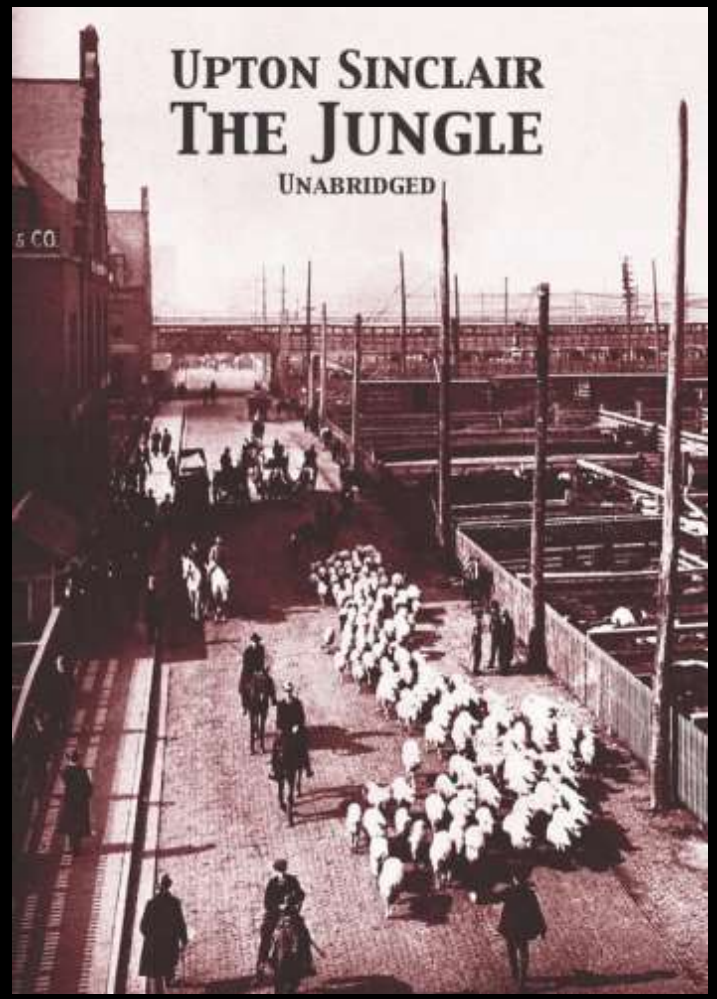
The Historical Evolution of Relationships Between Human and Veterinary Medicine

One Medicine: (1850-1920)

- identification of common mechanisms of disease pathophysiology between animal species and humans
- health of horses, oxen as vital transportation and agricultural resources and military campaign logistics



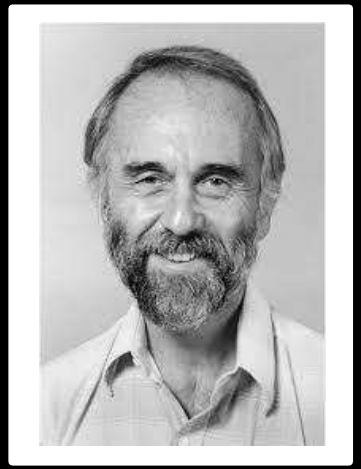

Reform of Food Safety in Early 20th Century



- food-borne illness as major cause of morbidity and mortality
- adverse economic impact on workforce needed to drive industrialized urbanization
- TB as dominant cause of reduced lifespan
- Food and Drugs Act (1906) and Meat Inspection Act (1906)
  - “prevent the manufacture; sale or transportation of adulterated or misbranded or poisonous or deleterious food drugs, medication and liquors”

The One Medicine: One Health Concept
A Fluctuating Momentum

James Steele
Founder,
Veterinary Public
Health Division, CDC
(1947)



Calvin Schwabe
UC Davis School of
Veterinary Medicine
(1967)

One Health
Initiative
(2006)

Ronald M. Davis
AMA
One Health
Resolution
(2007)

AVOHS
American Veterinary One Health Society

The Historical Evolution of Relationships Between Human and Veterinary Medicine

1910 Onwards: Progressive Uncoupling

- rise of the combustion engine and mechanized agriculture
  - closure of many Colleges of Veterinary Medicine and shift to focus on agriculture/food production and safety
- Flexner report on Medical Education (1910)
  - increased focus on basic sciences and laboratory courses in medical training
- parallel growth of basic research departments in academia
- inbred laboratory mouse established (1907) and adoption as predominant model for experimental studies
- concept of comparative medicine viewed increasingly through the scientific lens of rodent disease models
- 1950s onwards: increased societal affluence, discretionary income and rapid growth in companion animal populations

The Evolution of Laboratory Models of Human Diseases

- rise of inbred laboratory animal disease models as core element of biomedical research and regulatory standards for preclinical safety testing of Rx, vaccines, devices
- neglected opportunity for leadership by veterinary schools and void filled by new Departments of Comparative Medicine in University Medical Schools/
  Life Sciences Schools
- veterinarians relegated to lab animal husbandry support and service roles rather than integral intellectual contributors in driving of new research initiatives
- ‘lost opportunity’ for veterinary research scientists with veterinary schools focused increasingly on companion animals and agricultural livestock

Large-Scale Laboratory Rodent Facilities with Sophisticated QA/QC inventory and Biocontainment Controls

Expansion of Murine Genetics, the Design Specialized Animal Models and Targeted Genetic Modification

Large-Scale Use of Rodents in Biomedical Research

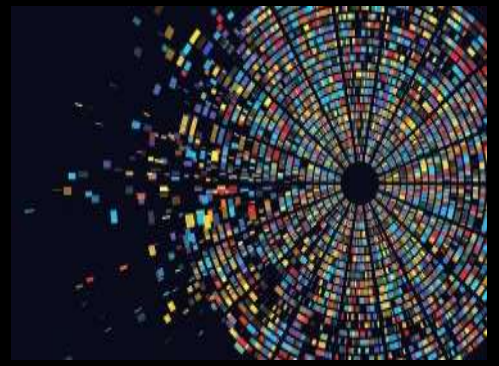
- multibillion dollar supply industry for academic, government and private sector research
- mandatory compliance with regulatory statutes for safety testing (and ideally also efficacy evaluation) of products/ingredients
  - human and veterinary medicine
  - diverse consumer products
  - environmental release and exposure risks
- targeted by animal welfare activists as part of broader campaign against toxicity testing of diverse animal-sourced products/ingredients

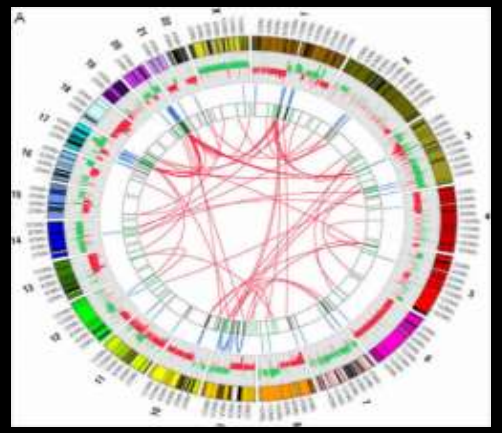
Precision Health

The Design of Health Interventions to Reflect the Unique Features of Disease Risk, Onset and Progression in Individuals and Populations

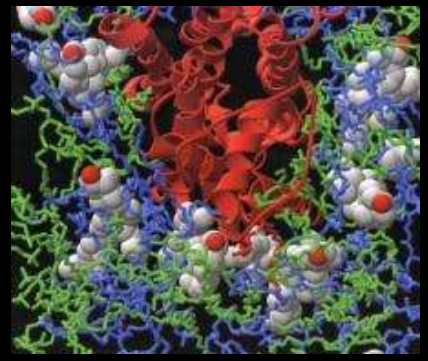
Precision Health and Deep Phenotyping: Mapping The Molecular Signatures of Disease as the Intellectual Foundation of Rational Diagnosis and Treatment Selection

(Epi)Genomics

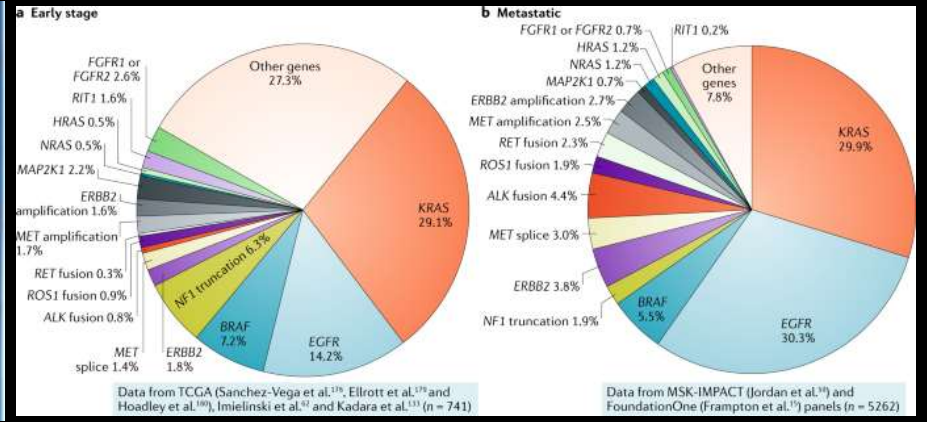




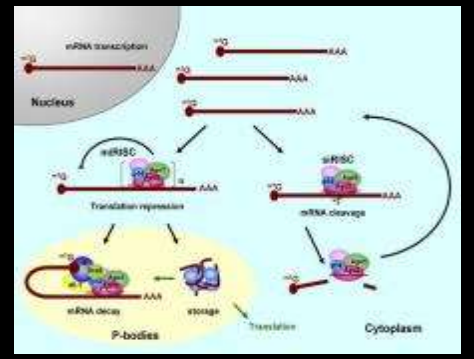
Proteomics



Molecular Pathways and Networks



Network Regulatory Mechanisms



ID of Causal Relationships Between Molecular Network Perturbations and Disease

Disease Subtyping Patient-Specific Disease Signatures: Disease Predisposition; R_x Selection; Disease Monitoring

Technology Trends in Human Healthcare
and
Diffusion into Veterinary Practice

Consumer Expectations for Highest Quality
Companion Animal Care as Powerful Economic Driver

vidium ANIMAL HEALTH

How can genomics benefit your cancer patients?

Knowing a tumor's genetic fingerprint can aid in the diagnosis and prognosis of cancer and help inform treatment decisions.

Learn more about SearchLight DNA™, an extensively validated diagnostic test from Vidium Animal Health® that uses next-generation sequencing to identify important mutations in 120 relevant cancer genes.

SearchLight DNA identifies important biomarkers to advance the care of pets with cancer

Discover how SearchLight DNA can provide insights into a cancer's origin, its behavior, and the optimal approach to treatment.

ONCOK9 | Overview for Pet Parents

PetDx

Finally, there is a blood test for **early cancer detection** in dogs

"Early detection and treatment are the best ways to manage cancer in pets... cancer is frequently treatable and early diagnosis will aid your veterinarian in delivering the best care possible.

- American Veterinary Medical Association

What is cancer screening?

Just like in people, cancer screening should be an important part of preventive care in dogs; the goal is to look for cancer when your pet is feeling well, before they start to show any clinical signs. During **wellness visits**, your

JAVMA

AVMA

Genomic tumor analysis provides clinical guidance for the management of diagnostically challenging cancers in dogs

Esther Chon, DVM, DACVIM*; Guannan Wang, PhD; Derick Whitley, DVM, DACVP; Sharadha Sakthikumar, PhD; Manisha Warrier, MS; Shukmei Wong, MS; Natalie Duran, MS; Jonathan Adkins, BS; Martin Boateng, BS; Zhanyang Zhu, PhD; Salvatore Facista, BS; David Haworth, DVM, PhD; William Hendricks, PhD

Vidium Animal Health, Translational Genomics Research Institute, Scottsdale, AZ

*Corresponding author: Dr. Chon (echon@vidiumah.com)

Received November 3, 2022
Accepted February 8, 2023

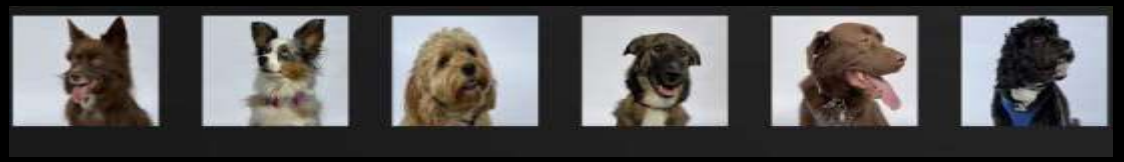
doi.org/10.2460/javma.22.11.0489

Canine Molecular Diagnostics: Disease Subtyping and Rx Selection

- Rx

- Rx

- Rx^r

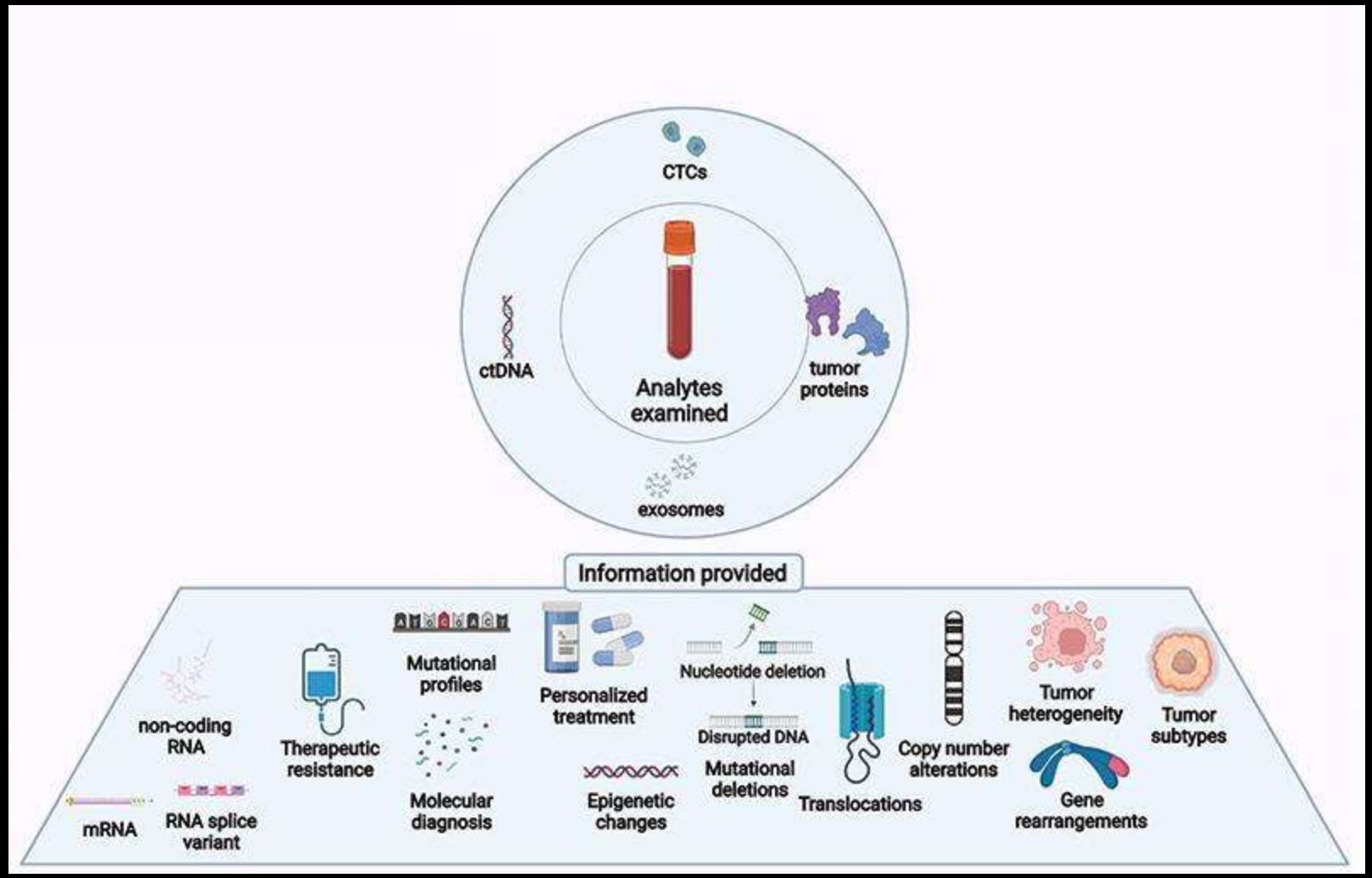


https://www.cbc.ca/news/business/marketplace-dog-dna-test-1.6763274

The Next Level of Large-Scale Holistic Data Integration for Comprehensive MultiOmics Profiling

- whole genome sequencing
- cell, tissue and individual-specific differential gene expression and transcription kinetics
- epigenetic modifications: DNA, histones and RNAs
- integrate effects of coding and non-coding regulatory variants across the entire genome
- transcription factor-promoter: enhancer interactions
- protein-RNA interactions
- RNA-RNA interactions
- chromosomal topologies/adjacencies chromatin interactions, gene neighborhoods and other long-range interactions (the 3-D genome)

The Rise of Blood-Based MultiOmics Profiling
The Liquid Biopsy



Minimally Invasive Canine Cancer Screening Platforms

PLOS ONE

Clinical validation of a next-generation sequencing-based multi-cancer early detection "liquid biopsy" blood test in over 1,000 dogs using an independent testing set: The CANcer Detection in Dogs (CANDiD) study

Andi Flory, Kristina M. Kruglyak, John A. Tynan, Lisa M. McLennan, Jill M. Rafalko, Patrick Christian Fiaux, Gilberto E. Hernandez, Francesco Marass, Prachi Nakashe, Carlos A. Ruiz-Perez, Donna M. Fath, Thuy Jennings, Rita Motalli-Pepio, Kate Wotrang, Angela L. McCleary-Wheeler, Susan Lana, Brenda Phillips, Brian K. Flesner, Nicole F. Leibman, Tracy LaDue, Chelsea D. Tripp, Brenda L. Coomber, J. Paul Woods, Mairin Miller, Sean W. Aiken, Amber Wolf-Ringwall, Antonella Borgatti, Kathleen Kraska, Christopher B. Thomson, Alane Kosanovich Cahalane, Rebecca L. Murray, William C. Kisseberth, Maria A. Camps-Palau, Franck Floch, Claire Beaudu-Lange, Aurélia Klajer-Peres, Olivier Keravel, Luc-André Fribourg-Blanc, Pascale Chicha Mazetier, Angelo Marco, Molly B. McLeod, Erin Portillo, Terry S. Clark, Scott Judd, C. Kirk Feinberg, Marie Benitez, Candace Runyan, Lindsey Hackett, Scott Lafey, Danielle Richardson, Sarah Vineyard, Mary Tefend Campbell, Nilesh Dharajiya, Taylor J. Jensen, Dirk van den Boom, Luis A. Diaz Jr., Daniel S. Grosu, Arthur Polk, Kalle Marsal, Susan Cho Hicks, Katherine M. Lytle, Lauren Holtvoigt, Jason Chibuk, Ilya Chorny, Dana W. Y. Tsui [view less]

Published: April 26, 2022 • https://doi.org/10.1371/journal.pone.0266623

JAVMA

AVMA

Clinical experience with next-generation sequencing–based liquid biopsy testing for cancer detection in dogs: a review of 1,500 consecutive clinical cases

Allison L. O'Kell, DVM, MS, DACVIM[1]; Katherine M. Lytle, DVM, MPH, MS[2]; Todd A. Cohen, DVM, DACVIM[1]; Lilian K. Wong, MS, DVM[1,3]; Emily Sandford, RVT[2]; Jill M. Rafalko, MS[1*]; Gina Brandstetter, DVM[1]; Lauren R. DiMarzio, DVM[1]; Ashley Phelps-Dunn, DVM[1]; Michelle C. Rosentel, DVM[1]; Chelsea D. Warren, DVM[1]; Angela L. McCleary-Wheeler, DVM, PhD, DACVIM[4]; Patrick C. Fiaux, PhD[5]; Francesco Marass, PhD[5]; Maggie A. Marshall, MS[5]; Carlos A. Ruiz-Perez, PhD[5]; Kristina M. Kruglyak, PhD[5]; John A. Tynan, PhD[4]; Susan C. Hicks, MAS[6]; Daniel S. Grosu, MD, MBA[1]; Jason Chibuk, MS[1]; Ilya Chorny, PhD[5]; Dana W. Y. Tsui, PhD[4]; Andi Flory, DVM, DACVIM[1]

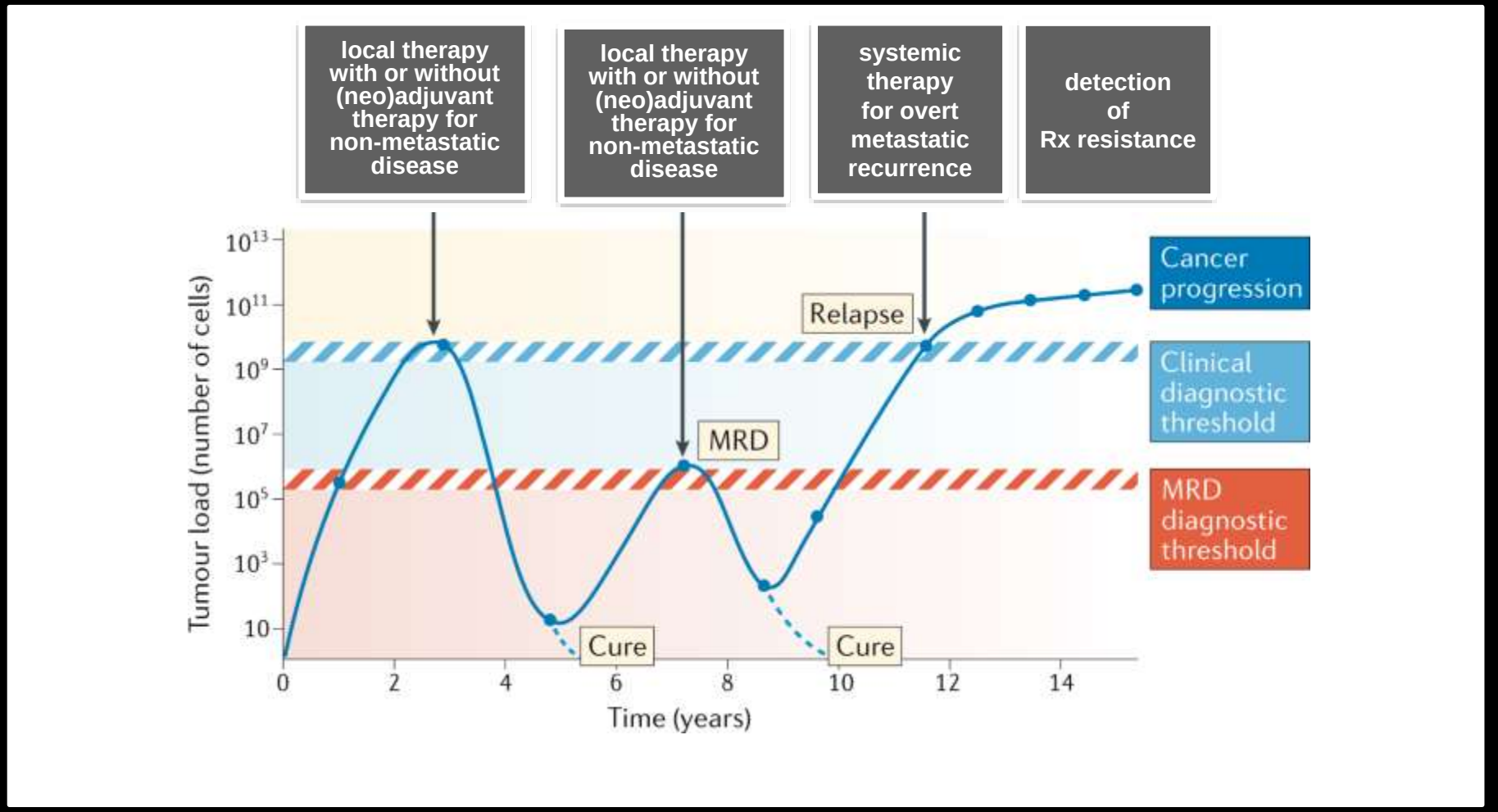
[1]PetDx, Medical & Clinical Affairs, La Jolla, CA
[2]PetDx, Customer Support & Success, La Jolla, CA
[3]Carlson College of Veterinary Medicine, Oregon State University, Corvallis, OR
[4]PetDx, Research Programs, La Jolla, CA
[5]PetDx, Information Technology, La Jolla, CA
[6]PetDx, Analytical Production, La Jolla, CA

*Corresponding author: Jill M. Rafalko, MS (jrafalko@petdx.com)

The Liquid Biopsy: Comprehensive Blood-Based MultiOmics Profiling

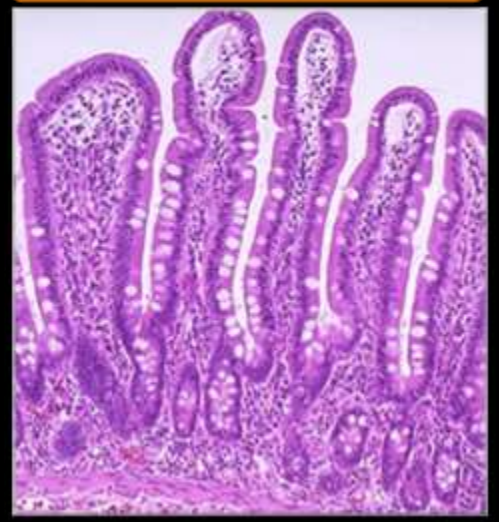
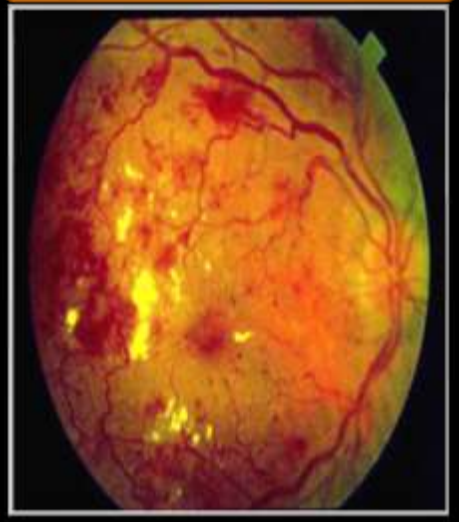
- oncology as initial focus but potential utility in diverse disease settings
- area of intense competition in human molecular diagnostics
  - over 65 companies
- lack of standardized methods as obstacle to cross-platform comparison
- ambitious agenda for multicancer early detection (MCED) tests
  - criteria for performance metrics and regulatory oversight of clinical utility (fit-for-purpose)

The Use of Cancer Liquid Biopsy Assays in Clinical Case Management



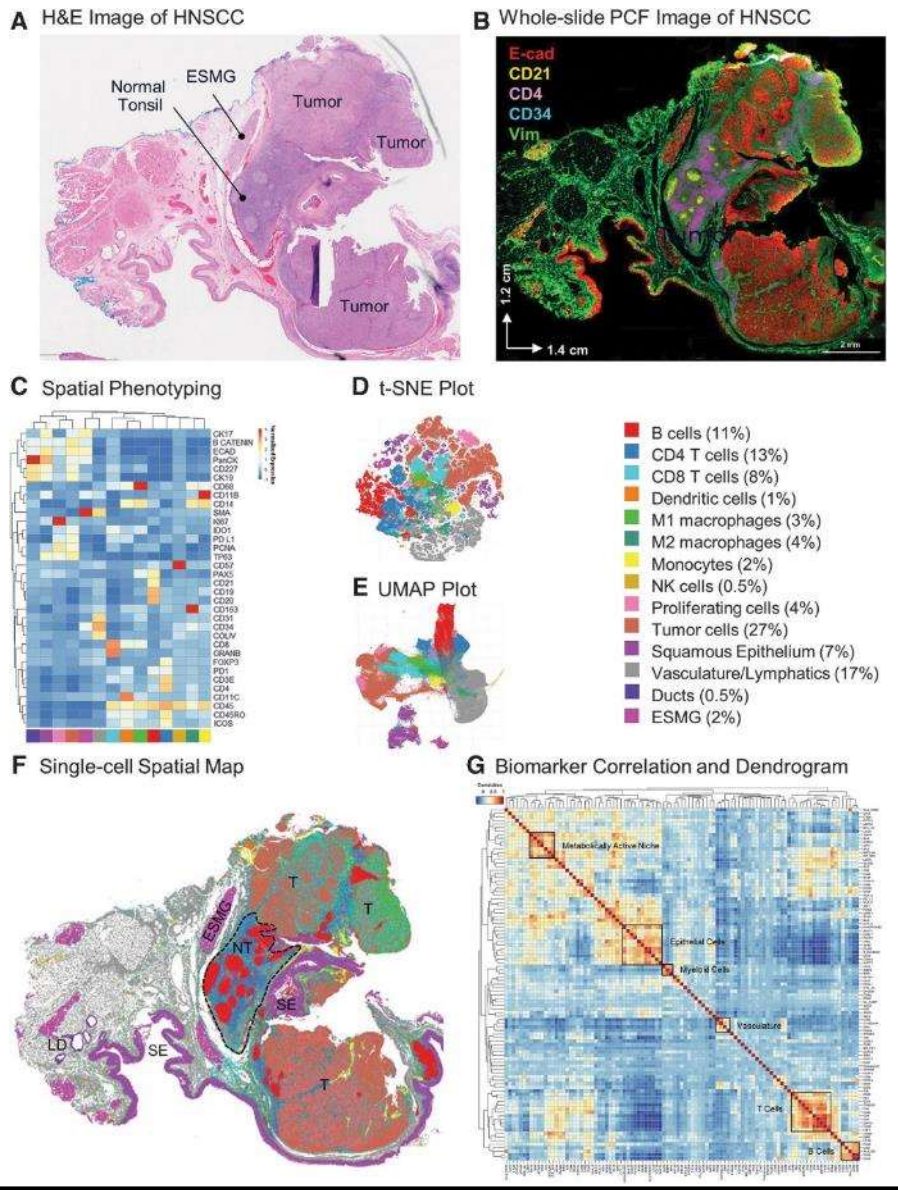
Adapted from: K. Pantel & C. Alix-Panabieres (2019) Nat Rev Clin Onc volume 16:409–424; doi.org/10.1038/s41571-019-0187-3

Machine Learning and Image Analysis in Clinical Medicine

pathology	radiology	dermatology	ophthalmology
			

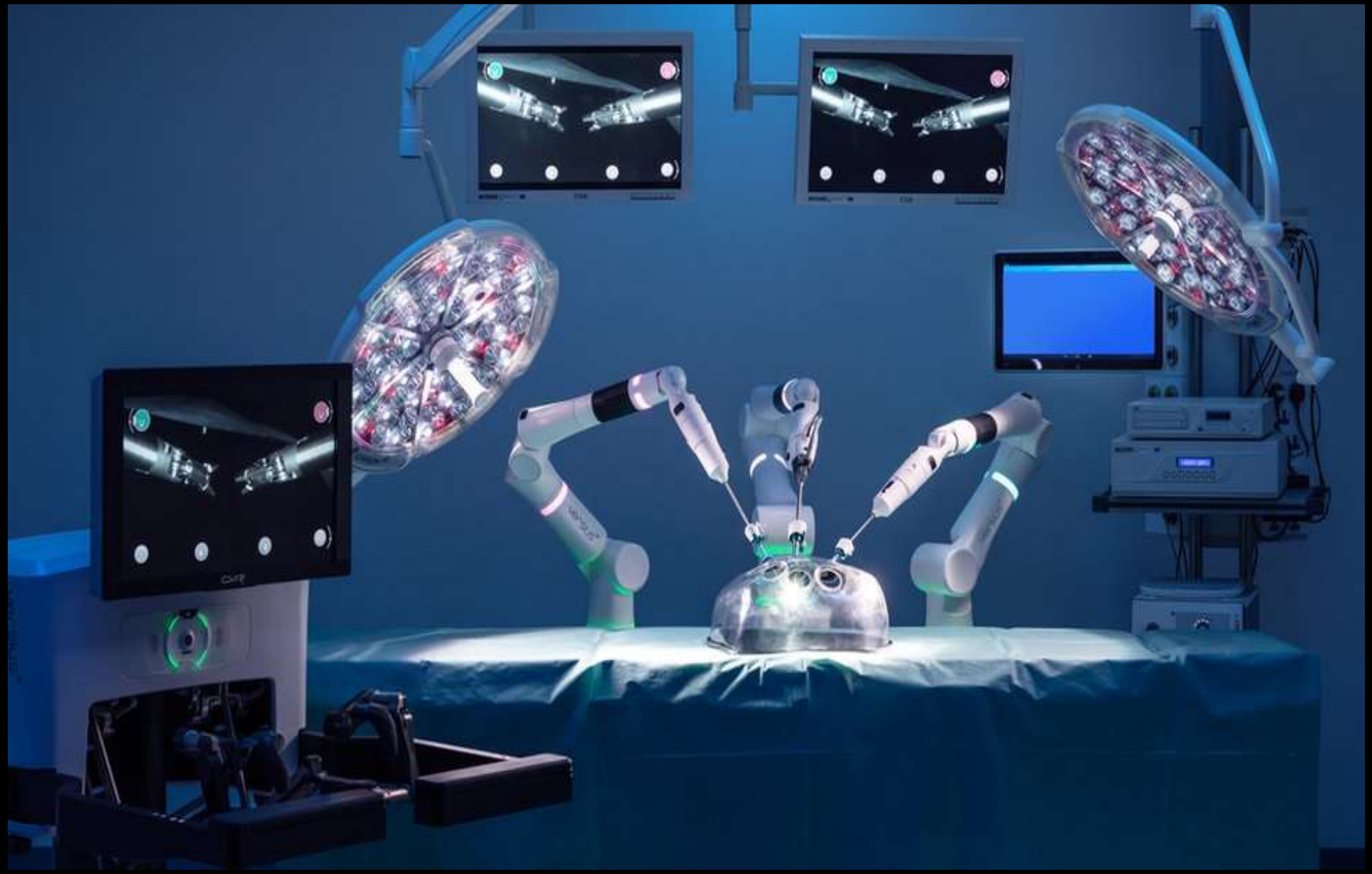
- large scale training sets and classification parameters
- standardized, reproducible and scalable
- 260 million images/day for $1000 GPU

101-Plex Spatial MultiOmics



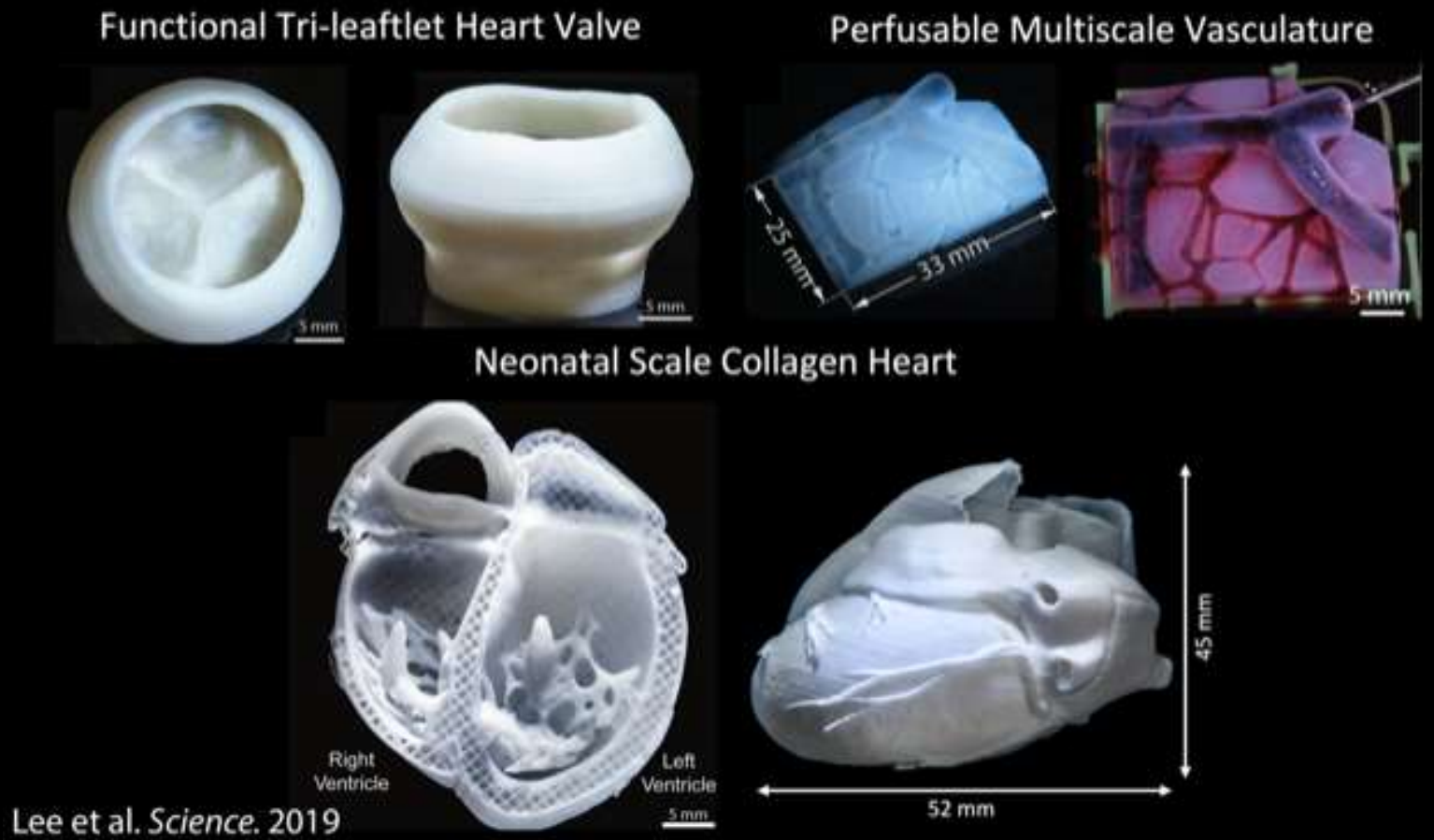
N. Jhaveri et. al. (2023) GEN Biotechnology 2:418-434; doi.org/10.1089/genbio.2023.0029

Predicted Cost Reduction in Automated Surgical Robotics: New Control Systems from Integration of Imaging with ML/AI Algorithms



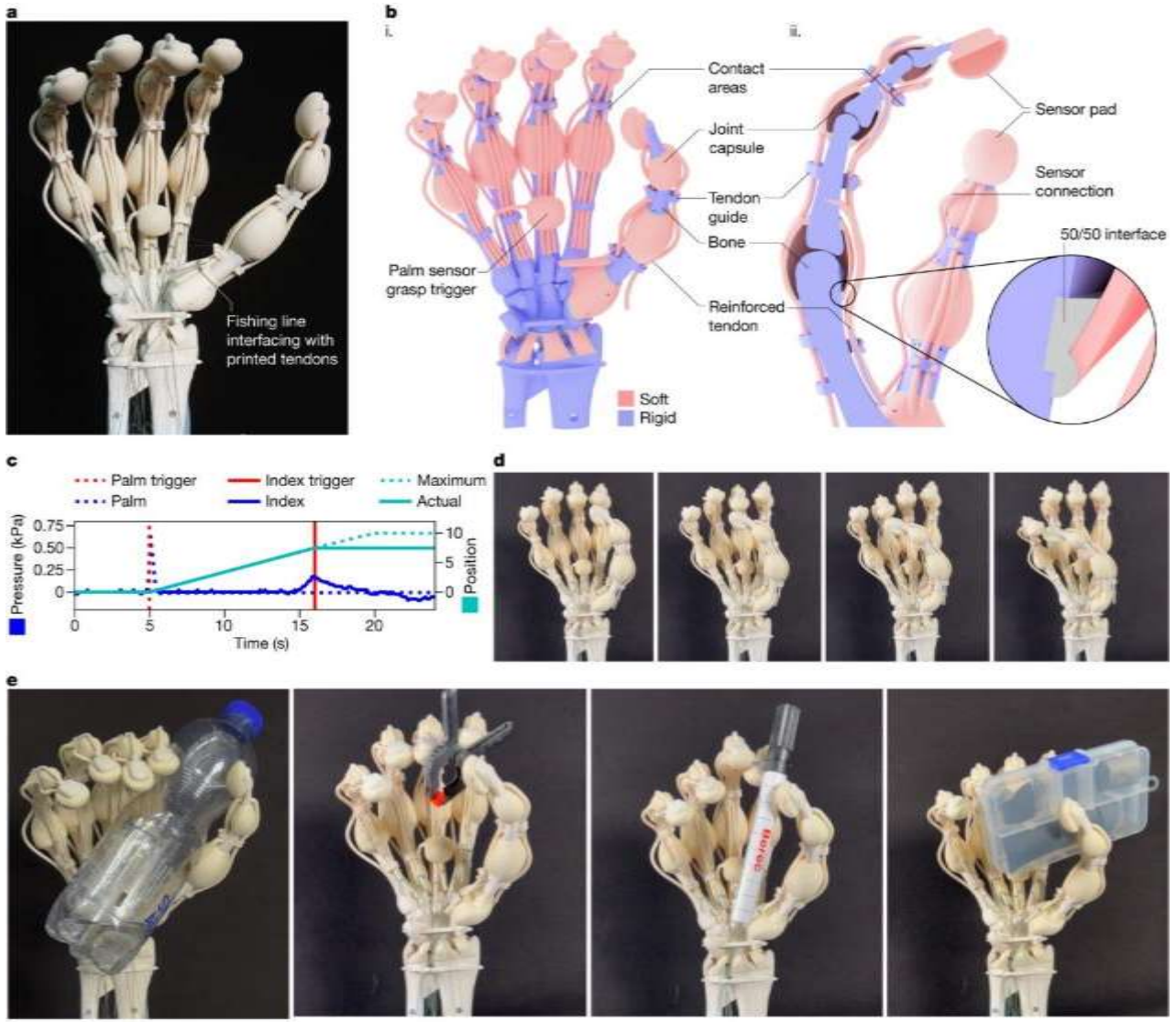
https://www.bbc.co.uk/news/health-45370642

3D Printing a Functional Tri-Leaflet Valve, Perfusable Vasculature, and Neonatal Scale Heart



https://engineering.cmu.edu/news-events/news/2022/10/18-3d-bioprinted-tissues.html

3D-One Process Manufacture of Sensorized Robotic Hand with Tendon-Driven Grip Capabilities



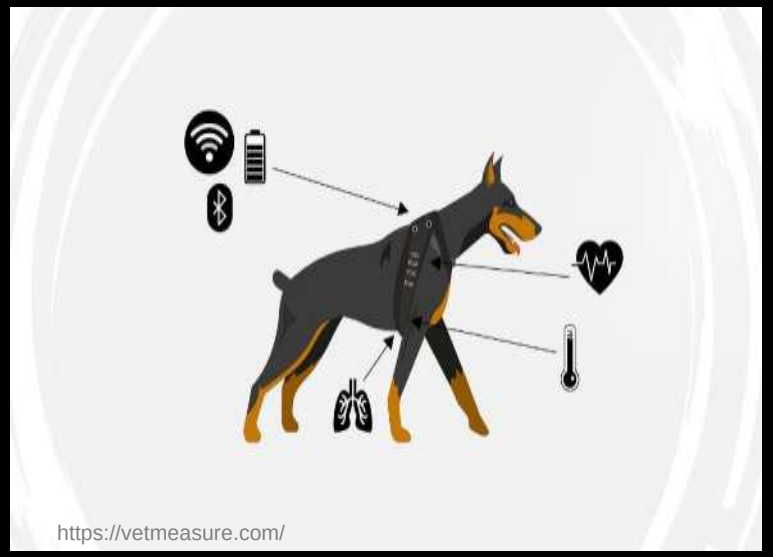
T.J.K. Buchner et. al. (2023) Nature 623:522–530; doi.org/10.1038/s41586-023-06684-3

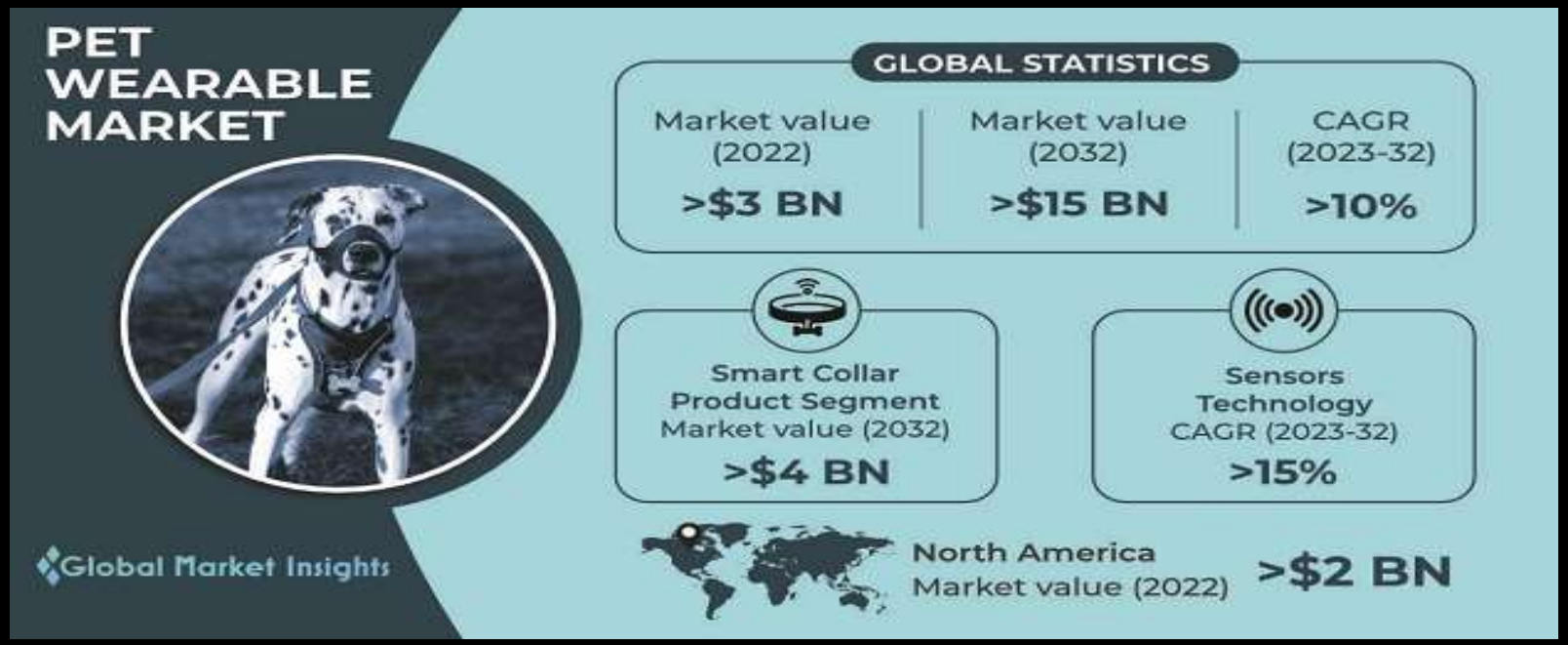
Health for Animals
global animal health association

DIGITAL REVOLUTION IN ANIMAL HEALTH

How Predictive, Monitoring and Diagnostics Technologies are Enabling Tailored Care and Better Welfare for Animals

The Connected Pet:
Telehealth and Remote Health Monitoring





https://www.gminsights.com/industry-analysis/pet-wearable-market

https://www.veterinarypracticenews.com/high-tech-remote-health-monitoring/

Telehealth and Remote Health Monitoring

- new sensor technologies for real time monitoring of health status
- integrated networks of multiple sensors for increasingly comprehensive clinical assessment
- faster detection of clinical deterioration and intervention
- monitoring treatment compliance and unanticipated adverse events
- longitudinal record of health status
  - individuals and populations
- ever larger databases for automated ML/AI analytics
  - proactive predictive risk analysis and mitigation
  - the digital twin concept: best match of individual patient profile to larger cohorts to optimize treatment options

NATIONAL ACADEMIES Sciences Engineering Medicine

Companion Animals as Sentinels for Predicting Environmental Exposure Effects on Aging and Cancer Susceptibility in Humans

Proceedings of a Workshop

AVMA | News

Silicone tags used to identify dogs' pollution exposures

Researchers see potential as a new tool for environmental monitoring

March 04, 2022

Evolution, Medicine, and Public Health [2023] pp.187–201
https://doi.org/10.1093/emph/eoad011
Advance access date 13 May 2023

ORIGINAL RESEARCH ARTICLE

EVOLUTION, MEDICINE, & PUBLIC HEALTH

Social determinants of health and disease in companion dogs: a cohort study from the Dog Aging Project

Brianah M. McCoy[1,2,†], Layla Brassington[1,2,†], Kelly Jin[3], Greer A. Dolby[4], Sandi Shrager[5], Devin Collins[6], Matthew Dunbar[7], Dog Aging Project Consortium[‡] and Audrey Ruple[8], Noah Snyder-Mackler[1,2,9,*]

Coalition for Connected Veterinary Care

Relationships first • Technology forward

AVMA | News

FDA to resume enforcement of all federal VCPR requirements for veterinary telemedicine

December 21, 2022

Telehealth bill advances in California Senate

Veterinary groups warn of unintended consequences to eliminating in-person requirement for establishing veterinarian-client-patient relationship

September 06, 2023
Updated November 1, 2023

frontiers | Frontiers in Veterinary Science

TYPE Opinion
PUBLISHED 10 October 2023
DOI 10.3389/fvets.2023.1245168

Can ChatGPT diagnose my collapsing dog?

Samira Abani[1,2*], Steven De Decker[3], Andrea Tipold[1,2], Jasmin Nicole Nessler[1] and Holger Andreas Volk[1,2]

[1]Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Hannover, Germany, [2]Centre for Systems Neuroscience, University of Veterinary Medicine Hannover, Hannover, Germany, [3]Department of Veterinary Clinical Science and Services, Royal Veterinary College, University of London, London, United Kingdom

GAI and the Rise of Chatbots in Healthcare

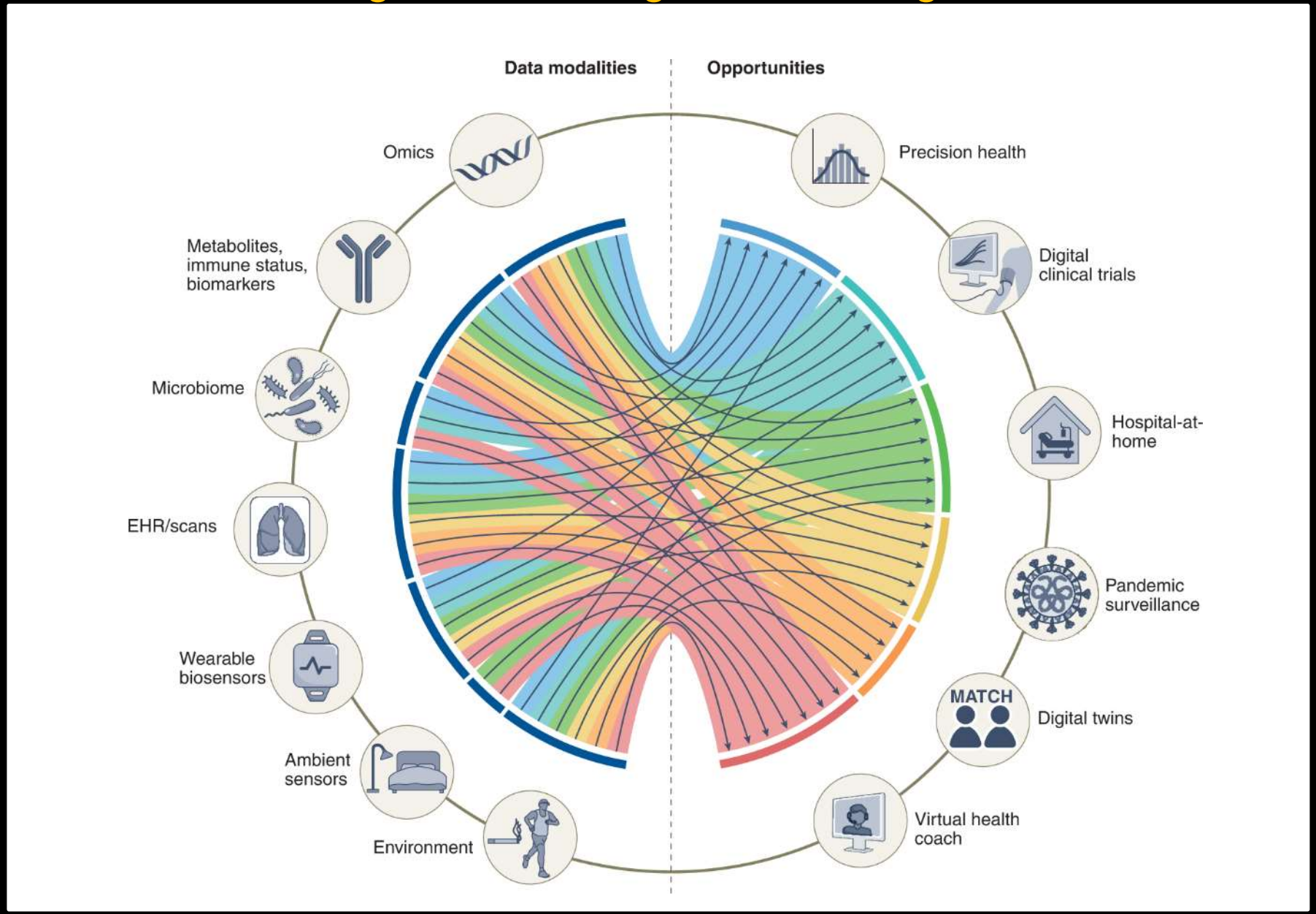
Adapted from B. Meskó & E. J. Topol (2023) NPJ Dig Med 6:120; doi.org/10.1038/s41746-023-00873-0

Human and Veterinary Medicine as Data-Intensive Disciplines

Evolution of Large-Scale Multimodal Databases

New ML/AI Analytics for Increasingly Automated Diagnosis and Clinical Decision Support Systems

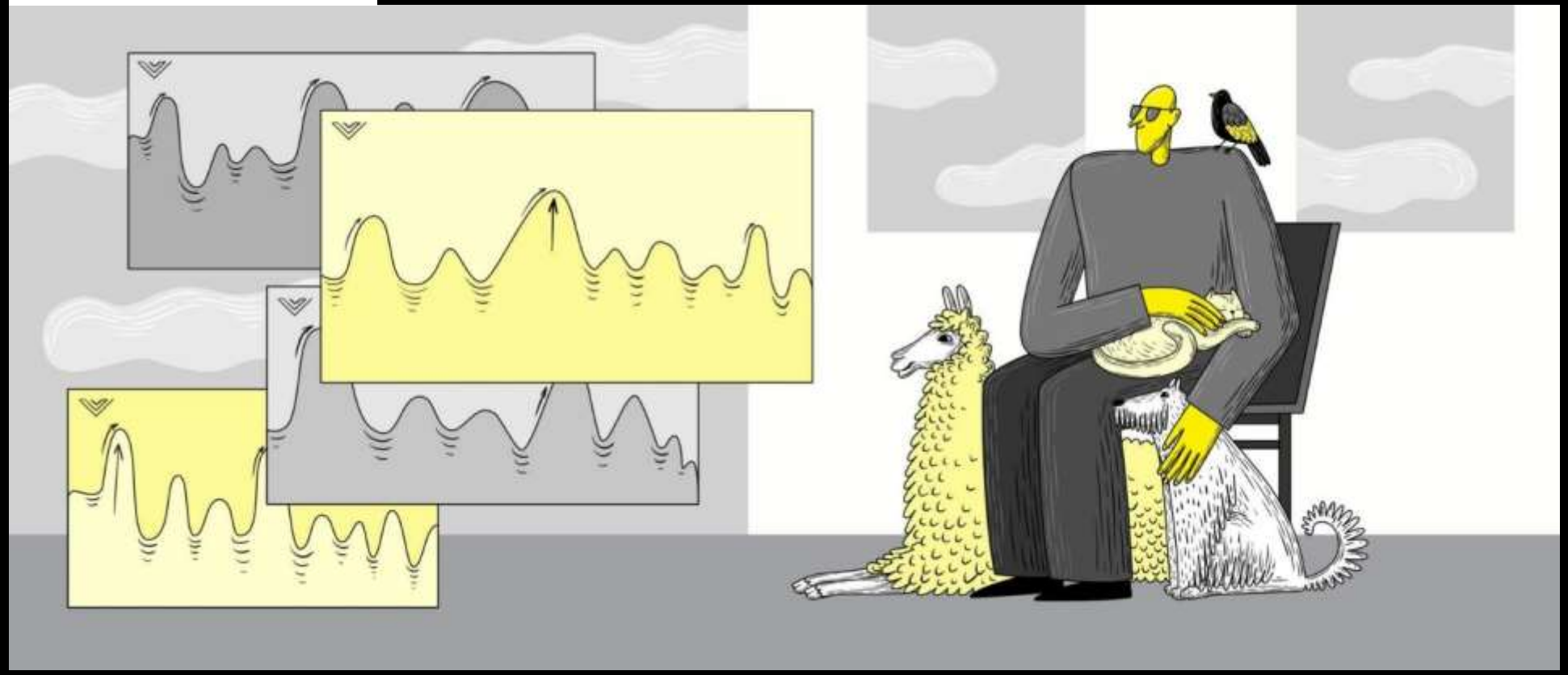
Precision Health and Deep Phenotyping: Multimodal Data Integration for Longitudinal Management of Health Risks



J.N. Acosta (2022) Nat Med 28, 1784

VETERINARY INTEGRATION SOLUTIONS

Veterinary Consolidators: North American Market Analysis



https://vetintegrations.com/insights/veterinary-consolidators/

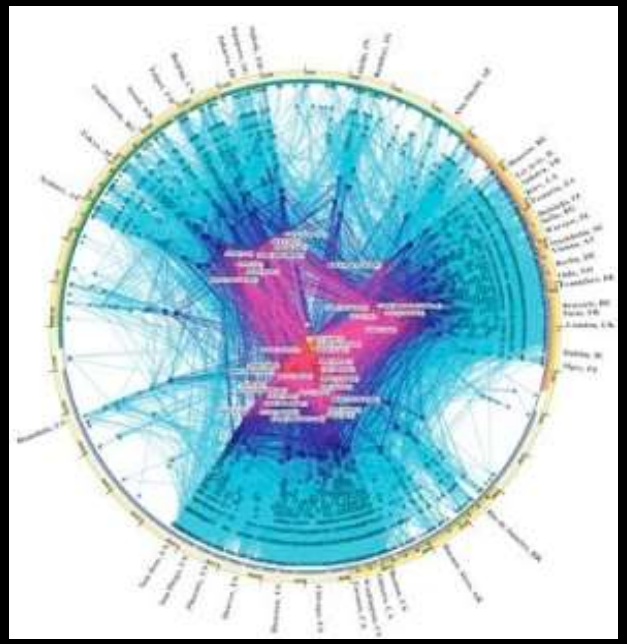
Continued Consolidation of Companion Animal Veterinary Clinics and Practices

Leverage Economies of Scale in Adoption of New Technologies and Increased Standardization of Data Capture Integration, Database Design and Cloud-Based Computing Infrastructure

The Emergence of Big Data and ML-AI Platforms Changes the Questions That Can Be Asked

Isolated Siloed Data

Complex Networked Data

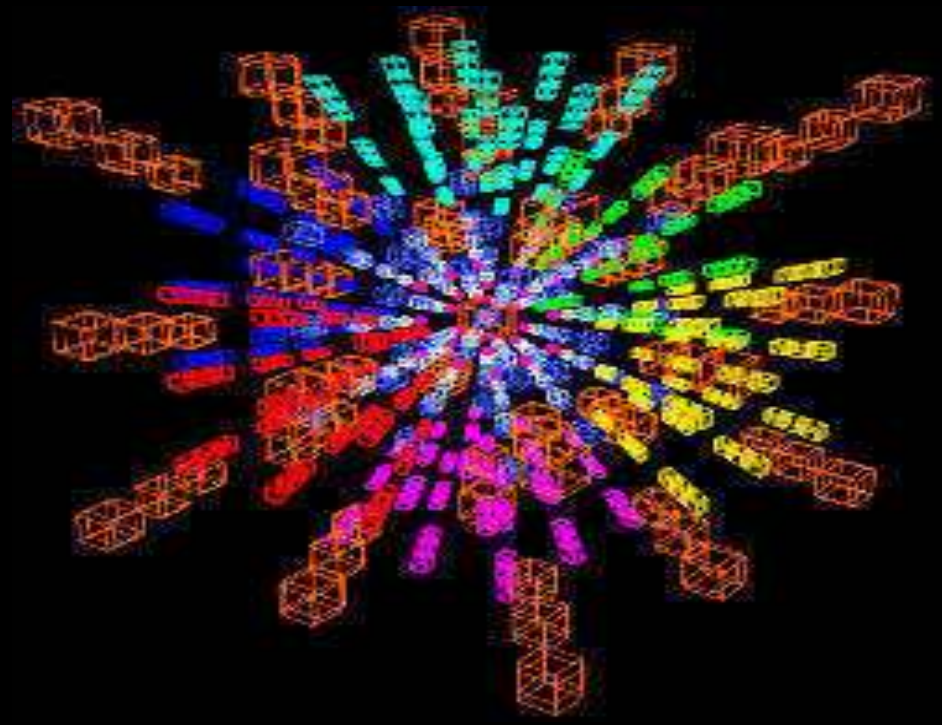


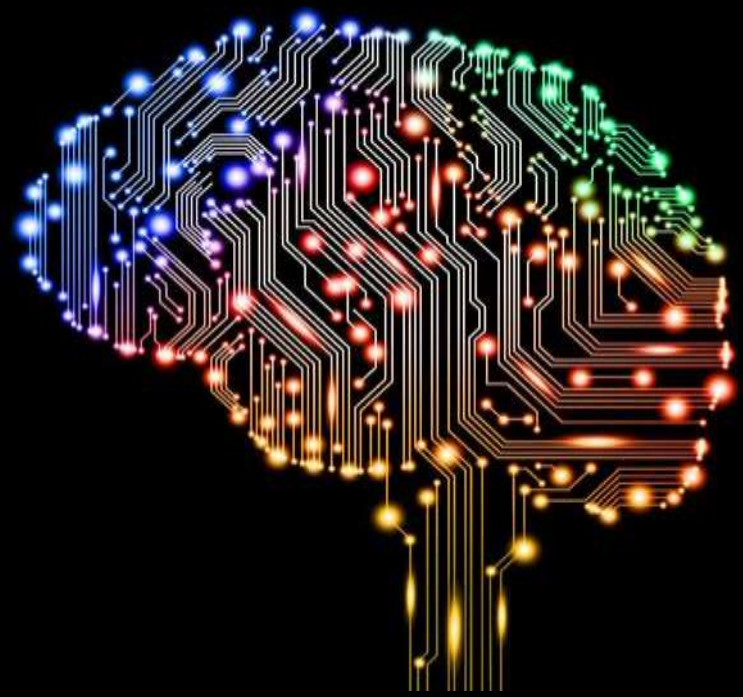
Complex Computational Data

Automated Learning Systems:
The Future of ‘Search’ and Decision Support

- deeper understanding of content and context structured text plus automated language processing of unstructured inputs
- search all things
  - integrate traditional document semantic sources with video, objects, speech
- why should you have to ask first?
  - smart machines and understanding where/what the user is doing
  - automated and proactive analytics
- why wait for the slow brain to catch up to the fast machine?

Automated Context: Data Finding Data
"Intelligence at Ingestion" and Collapse Time to Decision





Feature Extraction and Classification

Context Analysis

Persistent Context

- **Knowledge Topologies**
- **Learning Systems**

- **Data Fidelity**
- **Rapid, Robust Decisions**

Building ‘Digital Twins’:
Matching Individual Deep Phenotypes to ‘Best Fit’ Cohorts

Individual Data

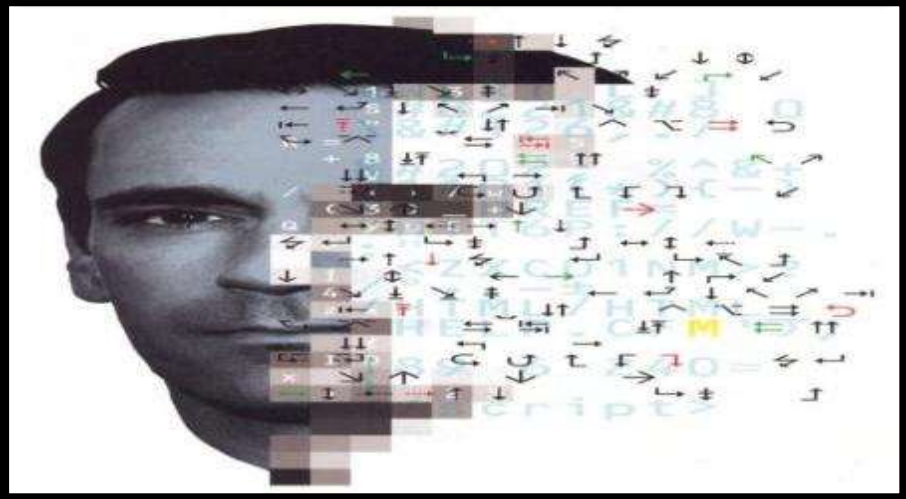
Population Databanks

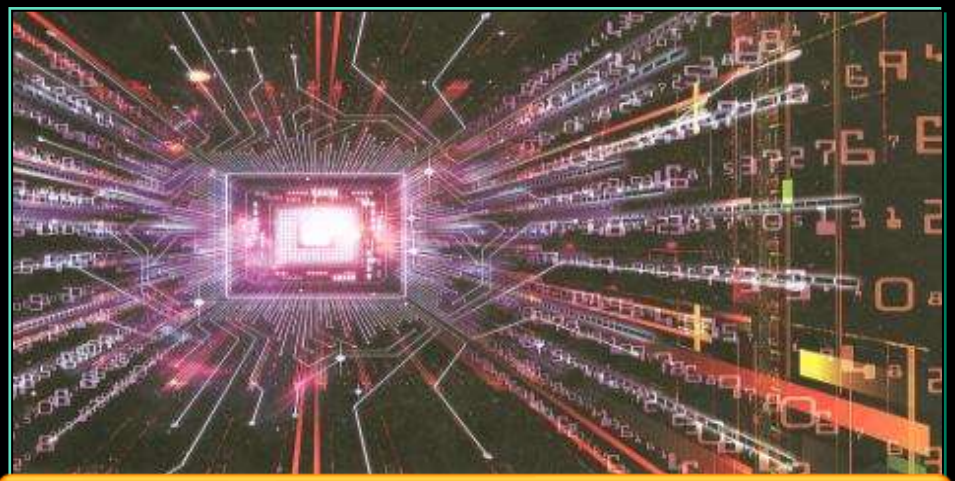
- digital twins and siblings’ and imputed phenotypes
- risk predisposition and disease prevention
- earlier detection of subclinical disease and mitigation
- selection of optimum treatment regimen for overt disease
- improved outcomes
- RWE/RWD and synthetic control arms for clinical studies

Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Medical Education

Data Deluge

Cognitive Bandwidth Limits





Automated Analytics and Decision Support

Facile Formats for Actionable Decisions

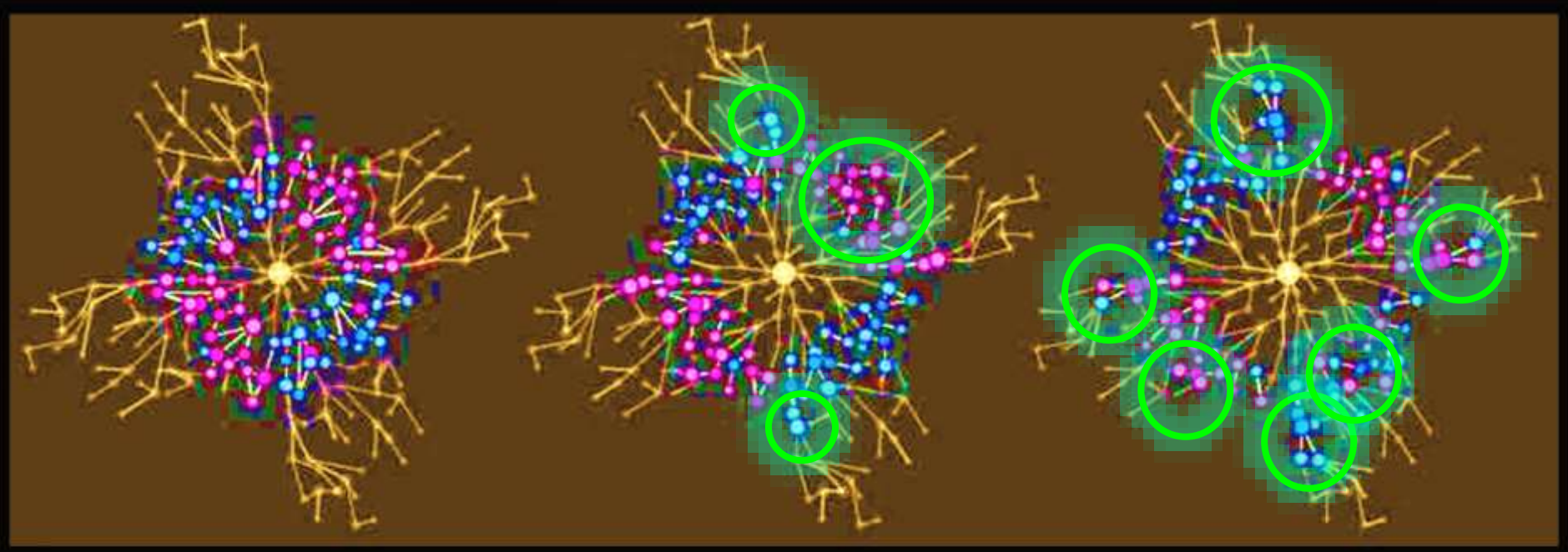
MultiOmics and Elucidation of Disease Mechanisms at the Molecular Level

The Intellectual Driver of Innovation in Precision Health

The Escalating Technical and Regulatory Complexity, Cost and Risk of Translational Research

The Need for New Paradigms in Preclinical Testing of Investigational Drugs to Constrain the Unsustainable Cost of Development Failures and Pricing of Approved Products

Diseases as Complex Adaptive Biological Systems: System State Shifts (Phenomes) and Cumulative Perturbations in Molecular Signaling Networks in the Health to Disease Continuum



$T_{1(n)}$ health	$T_{2(n)}$ subclinical disease	$T_{3(n)}$ overt disease

- identification of biomarkers/diagnostics and therapeutic targets in dysregulated networks
- DrugMechDB (2023) 4583 Rx indications, 5666 pathways
  32,249 molecular interaction networks across 14 biological parameters

Identification of New Therapeutic Targets

- multiOmics and major expansion of candidate targets
  - coding and non-coding elements
  - circular DNA
  - epigenetic targets
  - transcription factors, enhancers
  - splice variants
  - multiple RNA species
  - protein PTCMs
  - protein degradation pathways

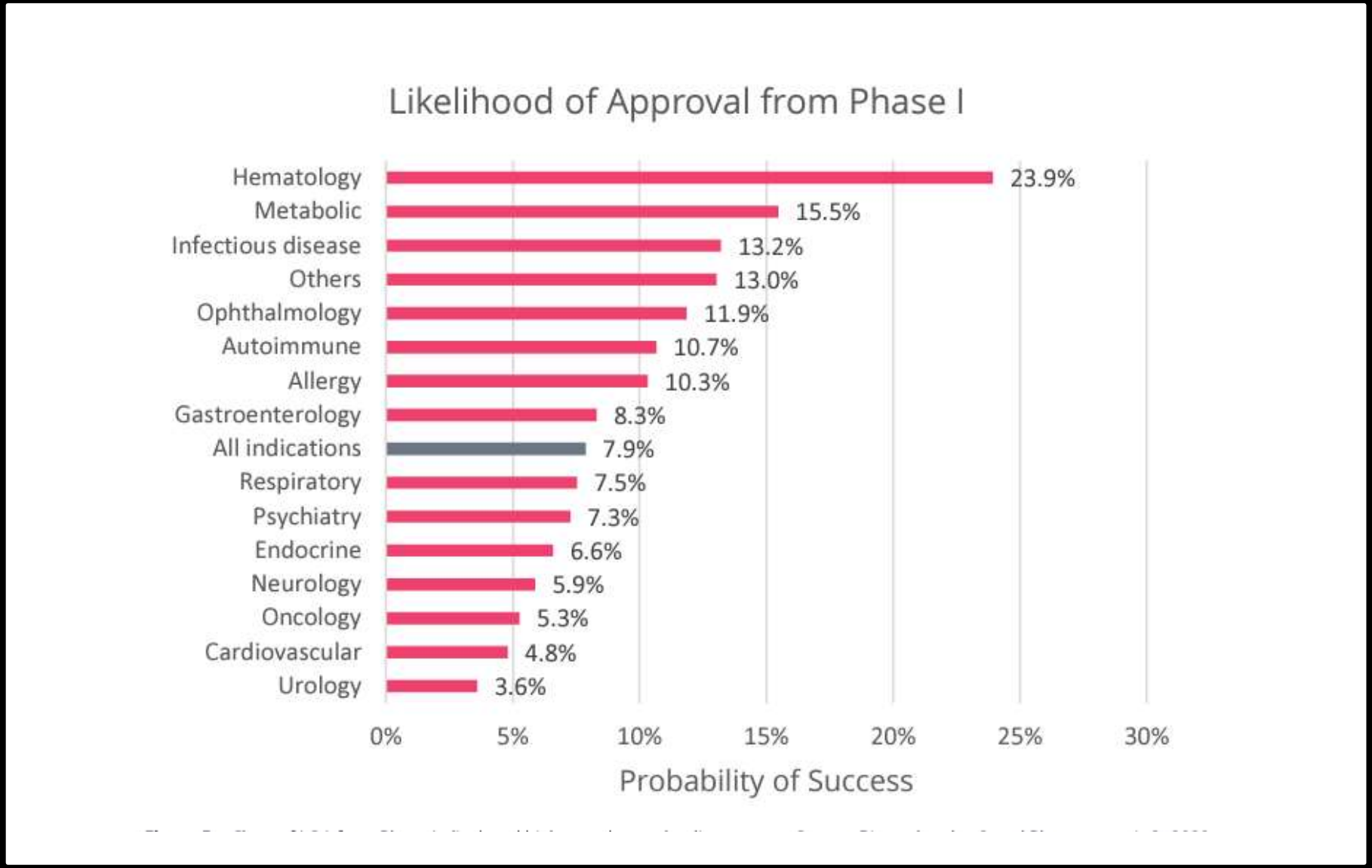
New Therapeutic Targets

- expansion of chemical drug classes
  - from small molecules to diverse biologicals
- biological drug classes
  - proteins
  - protein degraders (PROTACs), molecular glues
  - antibodies and antibody: drug conjugates (ADCs)
  - oligonucleotides and RNA therapeutics
  - gene therapies
  - cell therapies
  - exosomes
  - mRNA and saRNA vaccines
  - oncolytic viruses

The Persistent Achilles Heel in Proficient Translational Therapeutics Research

- the impressive research productivity in expansion of new drug targets and diversified drug classes has not been matched by advances in preclinical disease models to better predict drug efficacy in human clinical trials
- continued high rate of high-cost failure of investigational agents in Phase II/III clinical trials
- average cost of successful NDA/BLA now $1 to 3.8 billion
- inflation-adjusted cost has doubled every nine years

The High Failure of New Investigational Agents in Human Clinical Trials: Approval by Disease Area



https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf?_gl=1*8s30b5*_gcl_au*MTIxNjI0OTA1NS4xNjk3NjY0MTU0&_ga=2.102983811.2083123613.1697664154-1374498054.1697664154

JAMA Network Open.2023;6(7):e2324977

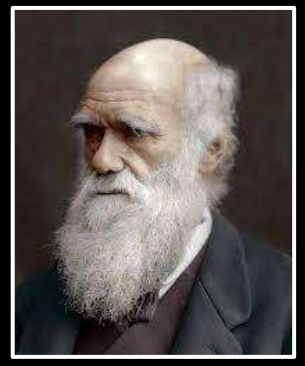
Original Investigation | Oncology

Costs and Causes of Oncology Drug Attrition With the Example of Insulin-Like Growth Factor-1 Receptor Inhibitors

Valerie Jentzsch, MSc; Leeza Osipenko, PhD; Jack W. Scannell, DPhil; John A. Hickman, DSc

- **16 inhibitors, 183 clinical trials, 12,000 patients in wide range of tumor types (2003 to 2021)**
- **no successful registrations**
- **estimated wasted clinical trial costs of $1.6 to 2.3 billion (plus risk exposure of patients)**
- **50% of the preclinical rodent tests demonstrated less than 50% tumor growth inhibition**

Failure and Waste in Biomedical Research:
Herd Mentalities in Scientific Research

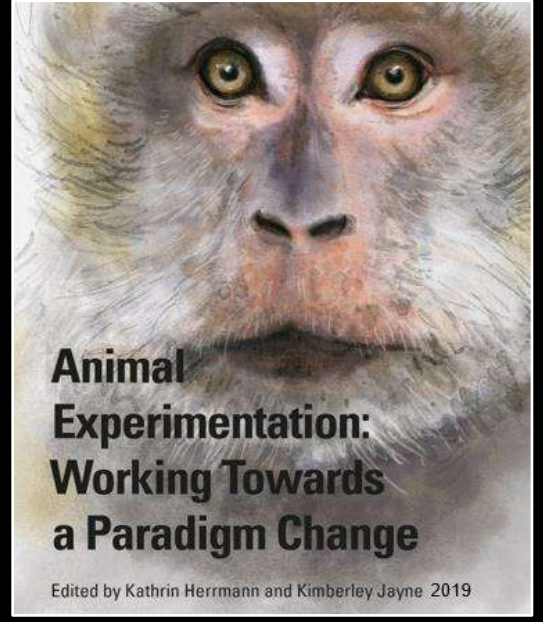


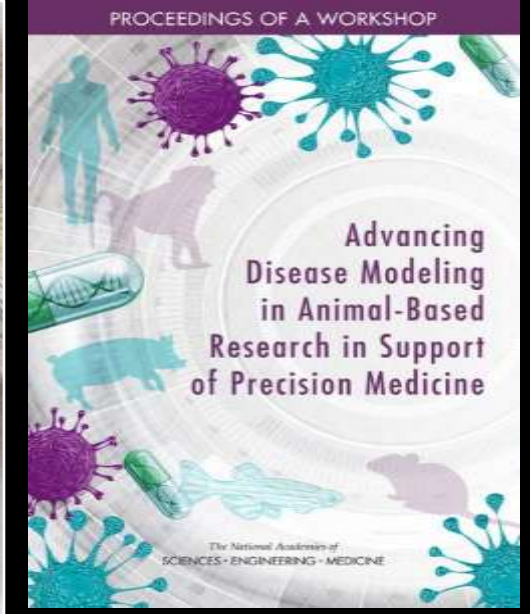
"To kill an error is as good a service as,
and sometimes even better than,
the establishing of a new truth or fact."

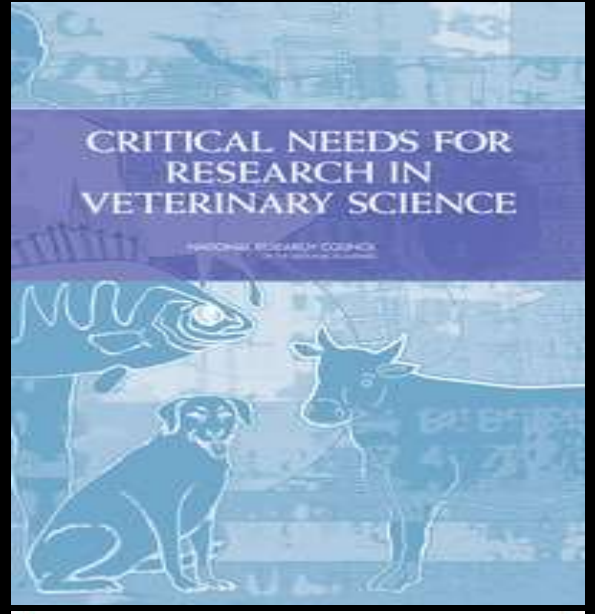
Charles Darwin 1879

"Animal research (or rodents) hasn't worked
and its time we stopped dancing around the problem
We need new methodologies for use in humans
to understand disease biology in humans.
You've lost the debate if you lose sight
of the taxpayers and the patients."

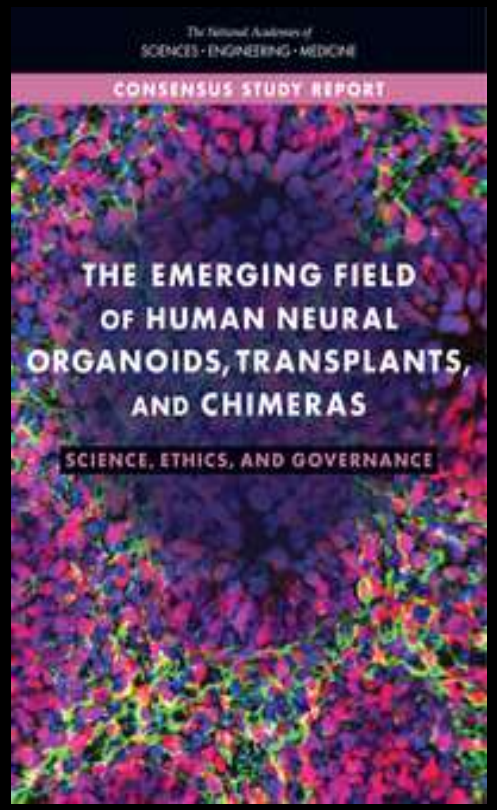
Elias Zerhouni, Director, NIH 2013


Animal Experimentation: Working Towards a Paradigm Change
Edited by Kathrin Herrmann and Kimberley Jayne 2019


PROCEEDINGS OF A WORKSHOP
Advancing Disease Modeling in Animal-Based Research in Support of Precision Medicine
The National Academies of SCIENCES · ENGINEERING · MEDICINE


CRITICAL NEEDS FOR RESEARCH IN VETERINARY SCIENCE


Proceedings of a Workshop
Therapeutic Development in the Absence of Predictive Animal Models of Nervous System Disorders
The National Academies of SCIENCES · ENGINEERING · MEDICINE


The National Academies of SCIENCES · ENGINEERING · MEDICINE
CONSENSUS STUDY REPORT
THE EMERGING FIELD OF HUMAN NEURAL ORGANOIDS, TRANSPLANTS, AND CHIMERAS
SCIENCE, ETHICS, AND GOVERNANCE


THE MISSING "R": REPRODUCIBILITY IN A CHANGING RESEARCH LANDSCAPE
A Workshop of the Roundtable on Science and Welfare in Laboratory Animal Use
(an ILAR Roundtable series)

The Limitations of Widely Adopted Laboratory Research Models in Replication of Pathophysiology of Major Human Diseases



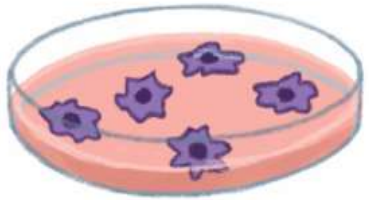

- inbred populations with constrained genetic heterogeneity
- truncated lifespans that do not reflect the biological heterogeneity of spontaneous disease processes in humans and outbred animal populations
- highly controlled laboratory environments and diets do not reflect real world environments
- failure to represent complex immune and CNS functions
- lack of pharmacological responses to human specific biologics

Trends in Preclinical Testing of Investigational Agents

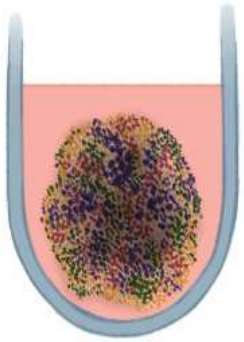
- FDA Modernization Act 2.0 (December 2022)
- pre-clinical testing on “non-relevant animals” no longer required for IND submission
  - animal data still accepted but non-animal-based test platforms can be used as alternates
  - in vitro and in silico methods

Use of In Vitro and In Silico Methods for Pre-IND Evaluation of Safety and Efficacy of Investigational Agents

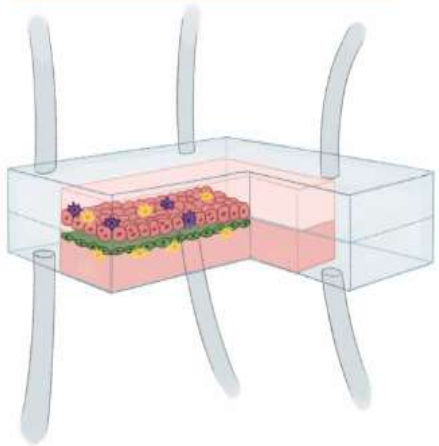
2D cultures → **3D organoids** → **microphysiological systems (MPS)** → … → **model multi-organ physiology**



- cells
- culture media, dishes, plates, wells
- extracellular adhesive proteins

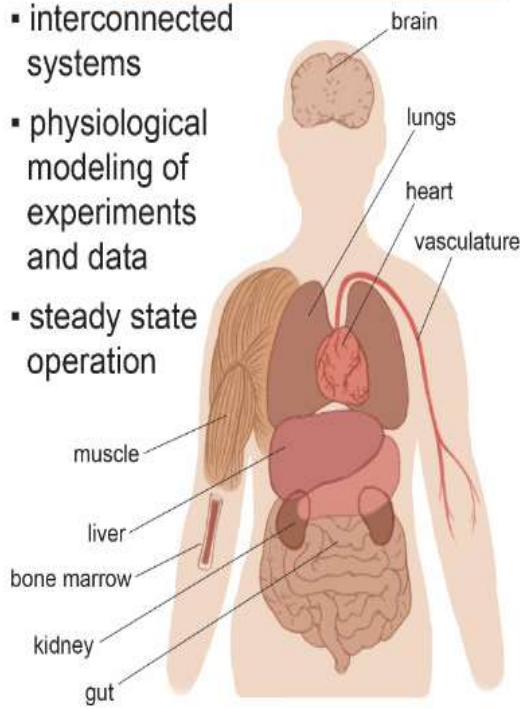


- multiple cell types
- cell-cell interactions
- extracellular proteins
- cell-induced extracellular remodeling



- organoid technology
- microfabrication of dedicated compartments
- microfluidic circulation of media

- interconnected systems
- physiological modeling of experiments and data
- steady state operation



https://www.fda.gov/drugs/regulatory-science-action/three-dimensional-3d-cell-culture-microphysiological-platforms-drug-development-tools

Trends in Preclinical Testing of Investigational Agents Regulatory Schizophrenia?

- long overdue recognition of historical evidence of poor predictability of rodent models of human disease
- legitimate question as to how far the proposed new roster of invitro methods will prove equally lacking due to failure to replicate complex histiotypic structures and multifunctional humoral and cell-mediated communication systems
- higher probability of value in safety (toxicity) profiling than efficacy assessment?

PINK SHEET
CITELINE REGULATORY

12 Oct 2023 | **Analysis**

Animal Models: Adcomm Exposes Internal Rift In How FDA Defines 'Translational' For Purposes Of Confirmatory Evidence

by Sue Sutter

FDA review staff consider the animal models used in development of US WorldMeds' eflornithine for neuroblastoma to be translational to humans, even though this does not align with the definition in a September 2023 draft guidance on types of confirmatory evidence.

Comparative Medicine 2.0

The Imperative for New Methods to De-Risk the Unsustainable High Cost of Failure of Investigational Products in Human Clinical Trials

Companion Animal Medicine as an Underleveraged Resource for Preclinical Profiling of New Human Investigational Products?

Arizona Comparative Medicine 2.0

- explore opportunities to build a comprehensive canine clinical trial network in Arizona
- validate testing in canine models to reduce unsustainable cost and frequency of failure of human candidate investigational agents in Phase II/III trials
- attract industry/regulatory funding
- increased revenue to clinics/practices from trial enrollment and monitoring
- reputational benefits with clients and expand client case
- enhanced professional clinical status from engagement in leading edge translational research in biomedicine

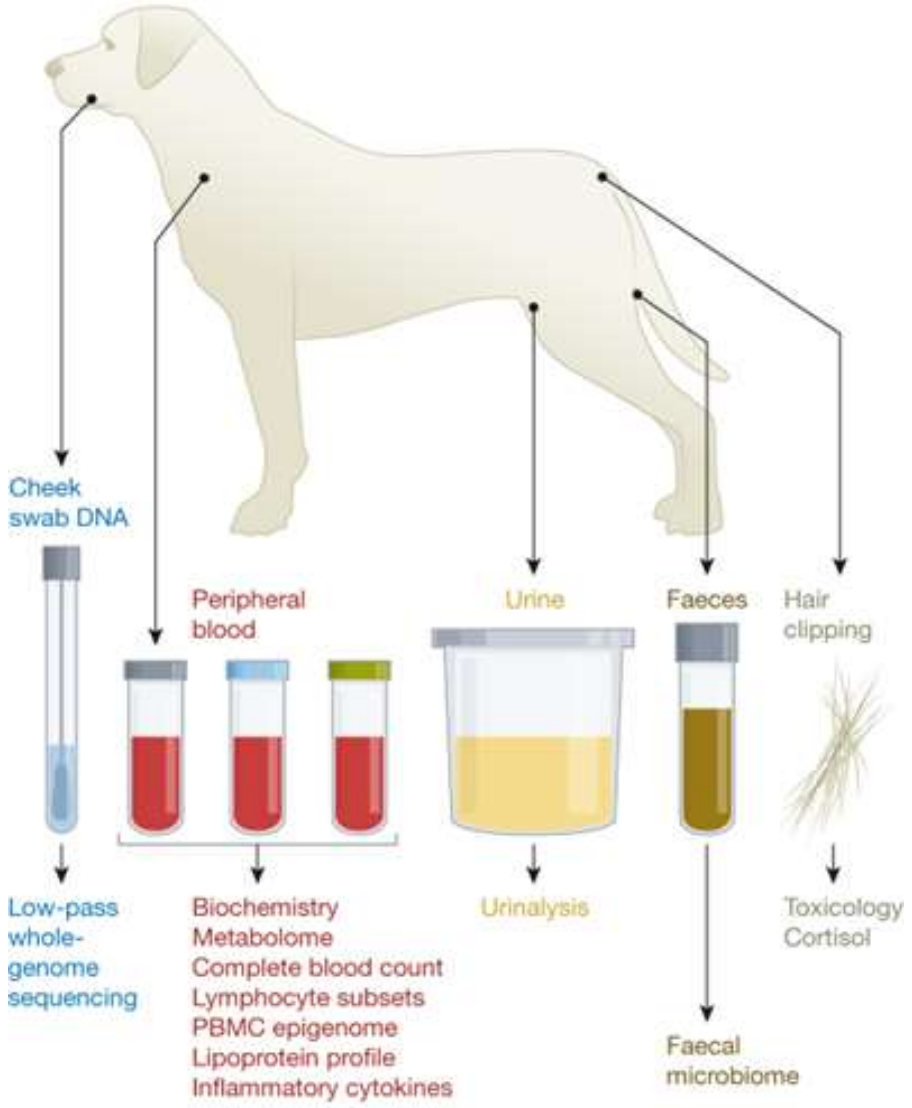
Companion Dogs as a Robust Translational Model for Biomedical Research

- shift away from traditional laboratory animal models to study more biologically relevant organisms that replicate pathophysiology of human disease
- appeal of companion dogs for systematic profiling of genetic (multiOmic), environmental and lifestyle factors affecting disease predisposition, disease onset and progression
- canine actuarial aging, aging trajectories and shared environmental exposure(s) as their human owners

Dog Aging Project

- interdisciplinary project involving over 20 academic institutions
- large scale longitudinal study
- diverse cohort of mixed breed and purebred dogs throughout their lifespan
- proactive engagement of dog owners and veterinarians
  - collection of biospecimens, clinical data, diet, physical activity, environment
- rigorous QA/QC of preanalytical variables in biospecimen analysis
- data from over 10,000 animals for low-pass WGS coverage
- residual samples archived at Cornell Veterinary Biobank with ISO 20387:28 compliance

Biospecimen Collection and Profiling in the Dog Aging Project



K.E. Creevy et. al. (2022) Nature 602:51–57; doi.org/10.1038/s41586-021-04282-9

Integration of Environmental Determinants with Biospecimen Profiling in the Dog Aging Project

American Community Survey

- Tract-level sociodemographic variables
- Neighbourhood economic variables

National Oceanic and Atmospheric Association

- County-level temperature measures
- County-level precipitation measures

Center for Air, Climate and Energy solutions

- Tract-level air pollution variables
- Four gases: O_3, CO, SO_2, NO_2
- Two aerosols: PM_{10}, $PM_{2.5}$

Neighbourhood walkability

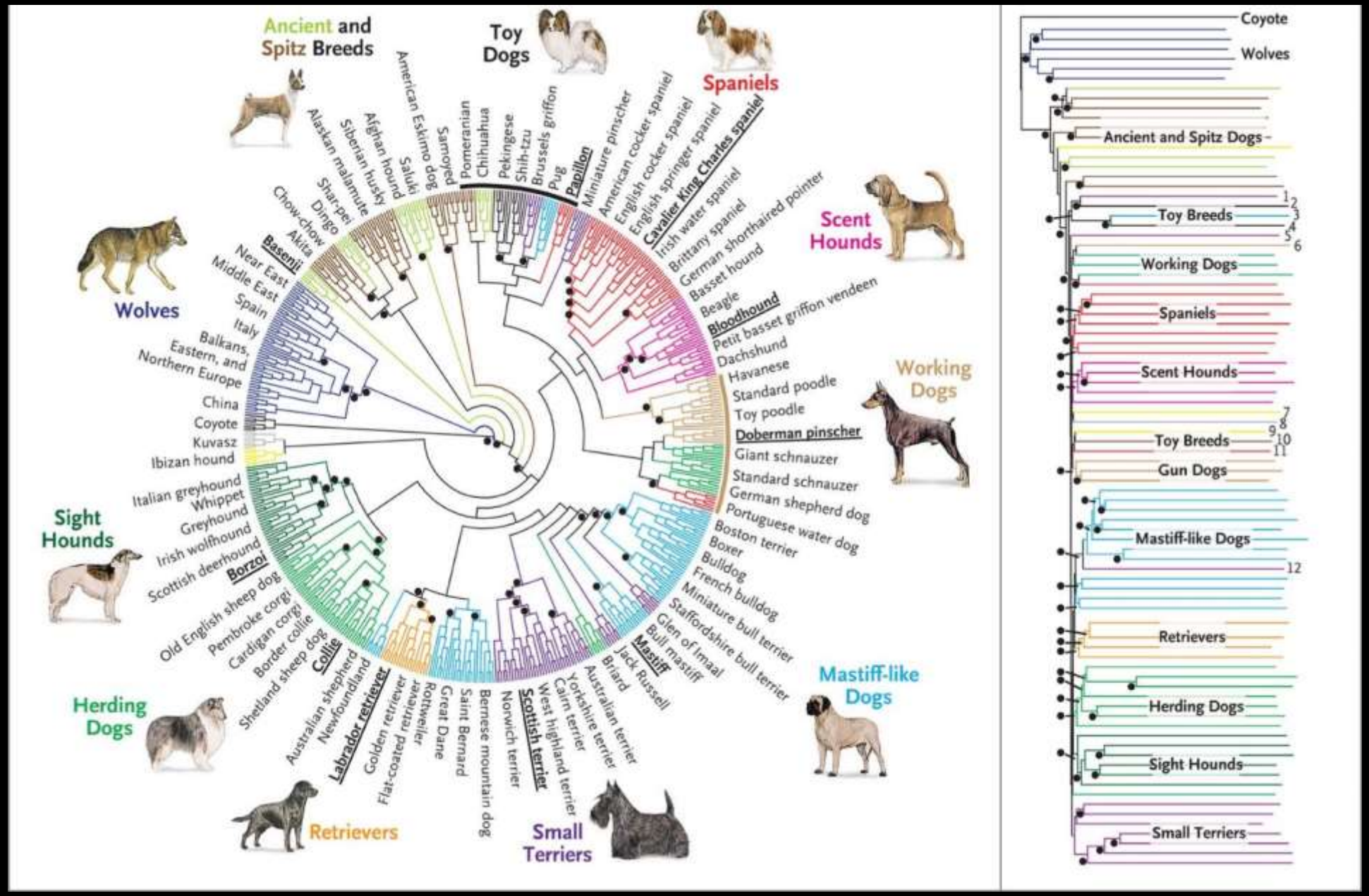
- Walkscore
- Tract-level residential density

K.E. Creevy et. al. (2022) Nature 602:51–57; doi.org/10.1038/s41586-021-04282-9

Chronic Late Onset Diseases in Companion Dogs As Clinical Trial Cohorts for Preclinical Evaluation of Candidate Interventions in Human Studies

- oncology
- obesity and diabetes (and cats)
- osteoarthritis and other orthopedic problems
- shortened lifespan
- cognitive decline
- decreased resilience to environmental warming

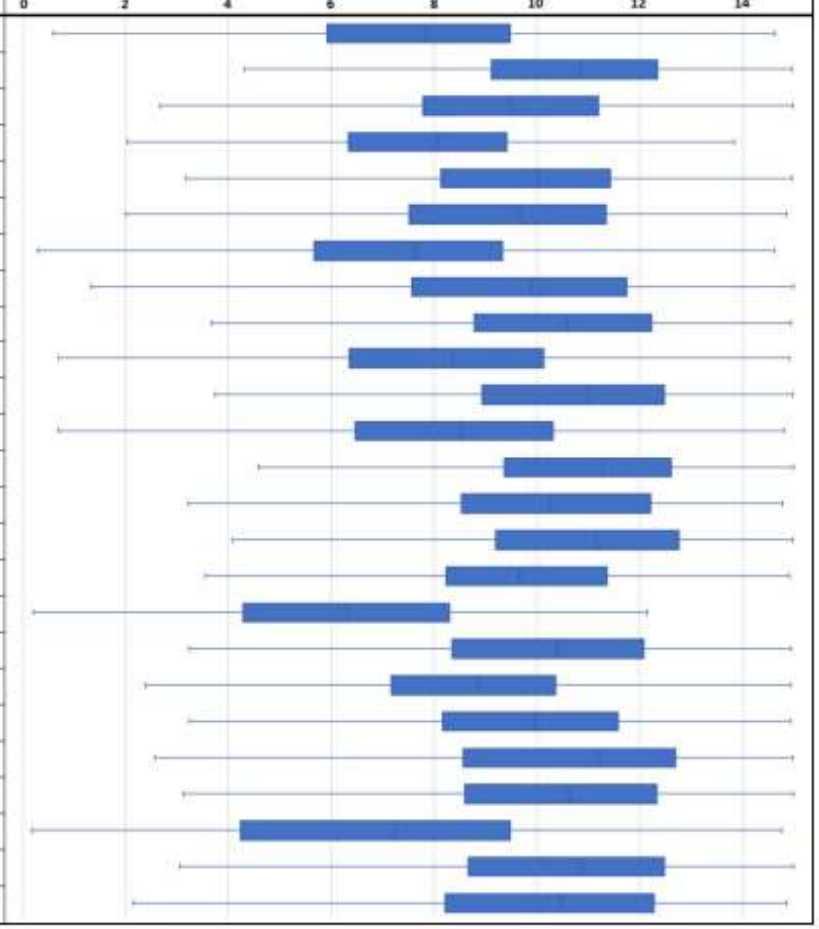
Canine Genetic Pedigrees



E. A. Ostrander (2012) N Engl J Med 367:636-646; doi.org/10.1056/NEJMra1204453

Relative Cancer Risk by Breed in Top 25 Most Popular Purebreds

1. Breed Name	2. Overall Relative Cancer Risk	3. Breed Popularity Rank	4. Average Age at First Cancer Claim	5. Age Distribution of First Cancer Claim
Boxer	261%	8	7.6	
Beagle	198%	18	10.5	
Golden Retriever	195%	2	9.2	
Rottweiler	183%	20	7.8	
Labrador Retriever	164%	1	9.5	
Boston Terrier	148%	19	9.3	
Doberman Pinscher	131%	25	7.4	
Pug	129%	15	9.4	
Schnauzer Miniature	118%	14	10.3	
English Bulldog	106%	7	8.0	
Maltese	96%	12	10.5	
American Pit Bull Terrier	95%	10	8.3	
Shih Tzu	94%	6	10.8	
Australian Shepherd	86%	22	10.0	
Dachshund Miniature	83%	11	10.7	
Cavalier King Charles Spaniel	81%	21	9.5	
Great Dane	81%	16	6.2	
Pembroke Welsh Corgi	80%	23	9.9	
German Shepherd	80%	4	8.5	
Siberian Husky	78%	13	9.6	
Poodle Toy	73%	24	10.5	
Yorkshire Terrier	69%	5	10.3	
French Bulldog	63%	3	6.8	
Chihuahua	52%	9	10.4	
Pomeranian	45%	17	10.0	



Benson, J., et al., *Diversity of Risk: Purebred Dogs and Cancer*. 2022: Nationwide.

Received: 9 May 2022 | Revised: 9 October 2022 | Accepted: 10 October 2022

DOI: 10.1111/vco.12863

Molecular phenotyping of malignant canine mammary tumours: Detection of high-risk group and its relationship with clinicomolecular characteristics

Vet Comp Oncol. 2023;21:73–81.

Mohamad Zamani-Ahmadmahmudi[1] | Maziar Jajarmi[2] | Saeedeh Talebipour[1]

Received: 31 January 2022 | Revised: 5 July 2022 | Accepted: 7 July 2022

DOI: 10.1111/vco.12848

Blood biomarkers for canine cancer, from human to veterinary oncology

Vet Comp Oncol. 2022;20:767–777.

Philippe Colombe[1,2] | Jérémy Béguin[2,3] | Ghita Benchekroun[2,4] | Delphine Le Roux[1,5]

Received: 10 May 2023 | Revised: 17 August 2023 | Accepted: 18 August 2023

DOI: 10.1111/vco.12935

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

Vet Comp Oncol. 2023;21:565–577.

Cheryl A. London[1] | Heather Gardner[1] | Shaying Zhao[2] | Deborah W. Knapp[3] | Sagar M. Utturkar[4] | Dawn L. Duval[5] | Melissa R. Chambers[6] | Elaine Ostrander[7] | Jeffrey M. Trent[8] | Gina Kuffel[9]

Received: 7 November 2022 | Revised: 26 April 2023 | Accepted: 8 May 2023

DOI: 10.1111/vco.12911

Standing in the canine precision medicine knowledge gap: Improving annotation of canine cancer genomic biomarkers through systematic comparative analysis of human cancer mutations in COSMIC

Vet Comp Oncol. 2023;21:482–491.

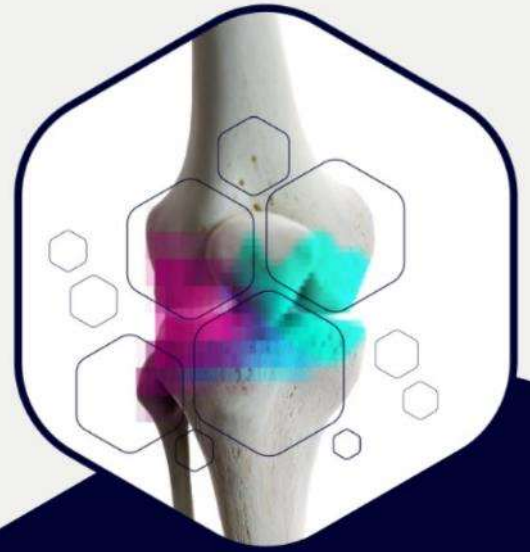
Sharadha Sakthikumar[1] | Salvatore Facista[1] | Derick Whitley[1] | Sara A. Byron[2] | Zeeshan Ahmed[1] | Manisha Warrier[1] | Zhanyang Zhu[1] | Esther Chon[1] | Kathryn Banovich[1] | David Haworth[1] | William P. D. Hendricks[1] | Guannan Wang[1]

ARPA-H

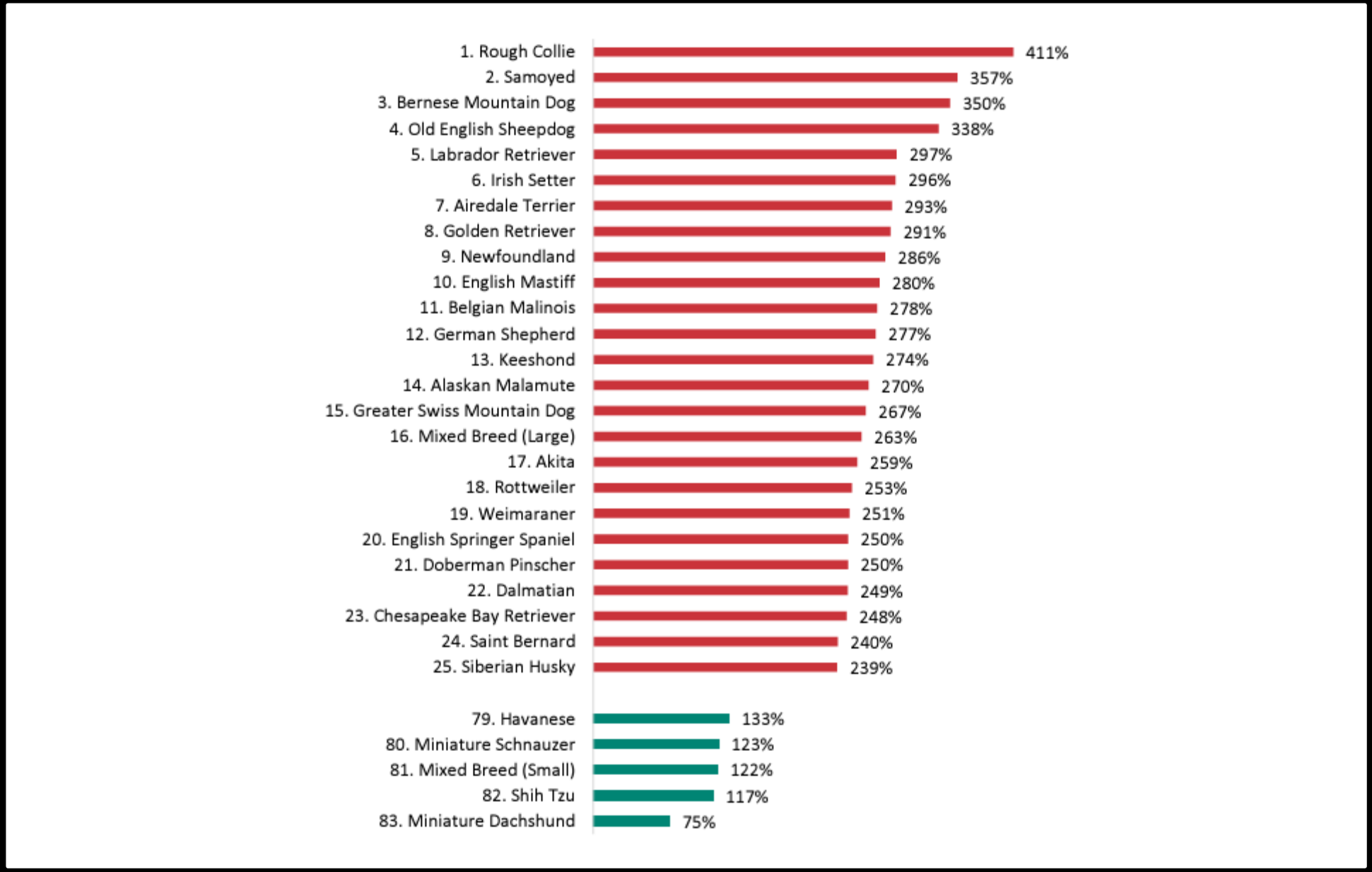
Imagine if
we could make
your joints
heal themselves?

NITRO

Novel Innovations for Tissue Regeneration in Osteoarthritis



Senior Life Stage Arthritis Relative Risk for 25 Highest-Risk and 5 Lowest-Risk Breeds



Nationwide.com

Stem Cells and Regenerative Medicine

JAVMA Currents in One Health
Leading at the intersection of animal, human, and environmental health
AVMA

A one-health perspective: use of hemoderivative regenerative therapies in canine and equine patients

Andris J. Kaneps, DVM, PhD, DACVS, DACVSMR*

Kaneps Equine Sports Medicine and Surgery LLC, Beverly, MA

*Corresponding author: Dr. Kaneps (ajkaneps@kanepsequine.com)

Received December 13, 2022
Accepted January 16, 2023

doi.org/10.2460/javma.22.12.0556

JAVMA Currents in One Health
Leading at the intersection of animal, human, and environmental health
AVMA

Use of mesenchymal stem cells for tendon healing in veterinary and human medicine: getting to the "core" of the problem through a one health approach

Lauren V. Schnabel, DVM, PhD, DACVS, DACVSMR[1,2]*, and Drew W. Koch, DVM, PhD, DACVS[1,2]

[1]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC
[2]Comparative Medicine Institute, North Carolina State University, Raleigh, NC

*Corresponding author: Dr. Schnabel (lvschnab@ncsu.edu)

GeroScience (2023) 45:1439–1450
https://doi.org/10.1007/s11357-023-00763-z

REVIEW

Banking on a new understanding: translational opportunities from veterinary biobanks

D. LaLonde-Paul · L. Moutthamm · Dog Aging Project Consortium · D. E. L. Promislow · M. G. Castelhano

Received: 25 May 2022 / Accepted: 3 January 2023 / Published online: 8 March 2023

Best Practices for Veterinary Clinical Studies

- federally funded animal research
  - Office of Laboratory Animal Welfare (OLAW) assurance and oversight by Institutional Animal Care and Use Committee (IACUC)
- FDA Center for Veterinary Medicine
  - GCP guidelines
  - 9/14/23 draft guidance for informed consent for enrollment of client-owned companion animals
- AVMA
  - Use of Veterinary Clinical Studies Committee
- CASTR Alliance
  - Companion Animal Studies for Translational Research Alliance

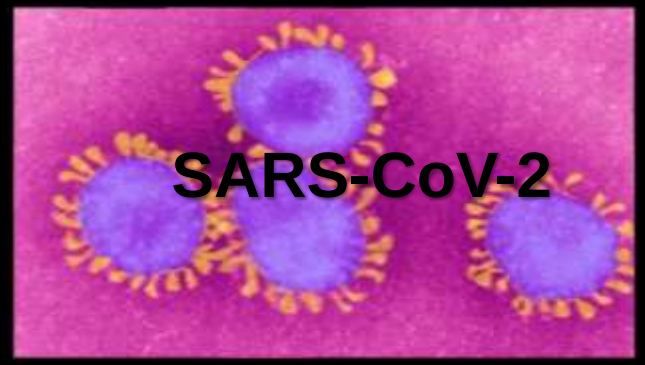
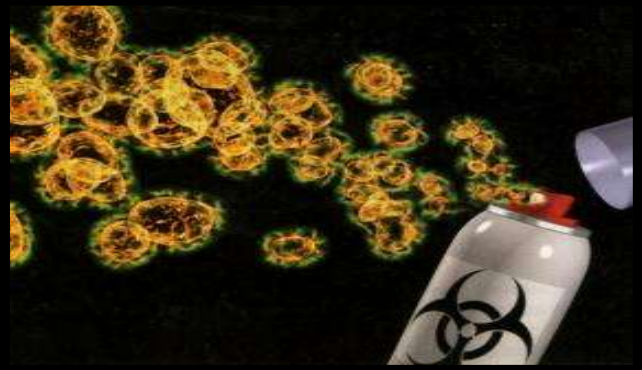
One Health

- an integrated, systems-based approach to optimize the health of people and animals, availability of crucial food resources and sustainable environmental ecosystems

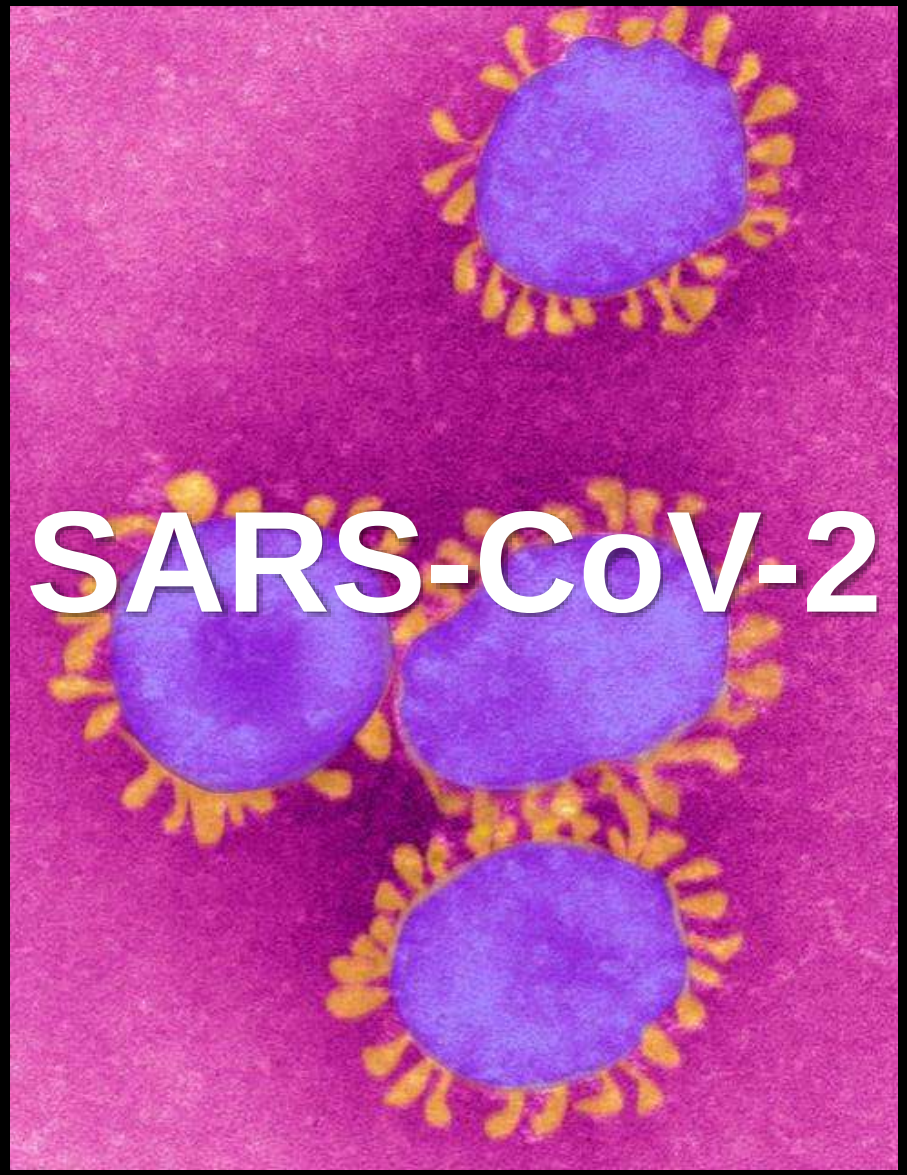
The ‘One Health’ Concept

- intimate and ever shifting interactions between human and animal hosts and environmental changes as drivers of risk
  - human health, agricultural productivity, food security
  - climate change: heat, drought, floods
  - socio-economic dislocations, political instabilities, conflict and geopolitical tensions
- still largely siloed operational activities and investment in different domains
  - public health for human populations
  - livestock and crop protection
  - environmental resiliency initiatives
- slow integration of one health as a core element of national/international public health policies and investment

The Relentless Ever-Changing Dynamics of Infectious Diseases

old foes resurgent: Rx – resistance	omnipresent pandemic threats	new foes: emerging infectious diseases
		
		
climate change and new vector ranges	**bioterrorism and bioweapons**	**dual-use research of concern**

What's Out There?
Comprehensive Global Biosurveillance and Preparedness for Epidemic/Pandemic Threats



Urbanization and Mega-Cities in Developing Countries and the Increased Threat of Zoonotic EIDs

High Population Density With Inadequate Biosurveillance

Expanded Eco-niches and New Zoonotic Exposures/Risks

Major Gaps in Health Infrastructure and Rapid Disease Reporting

Food Production Systems and Changing Infectious Disease Risks in Low-and Middle-Income Countries (LMICs)

- population growth, urbanization and consumer demand for meat-based diets
- intensification of livestock production
  - shift from rural smallholders to large periurban production units
- deforestation for livestock production expanded of encounters with zoonotic EID reservoir hosts

Expansion of Intensive Livestock Farming Processes and Inter-species Transmission of Antibiotic Resistant Plasmids

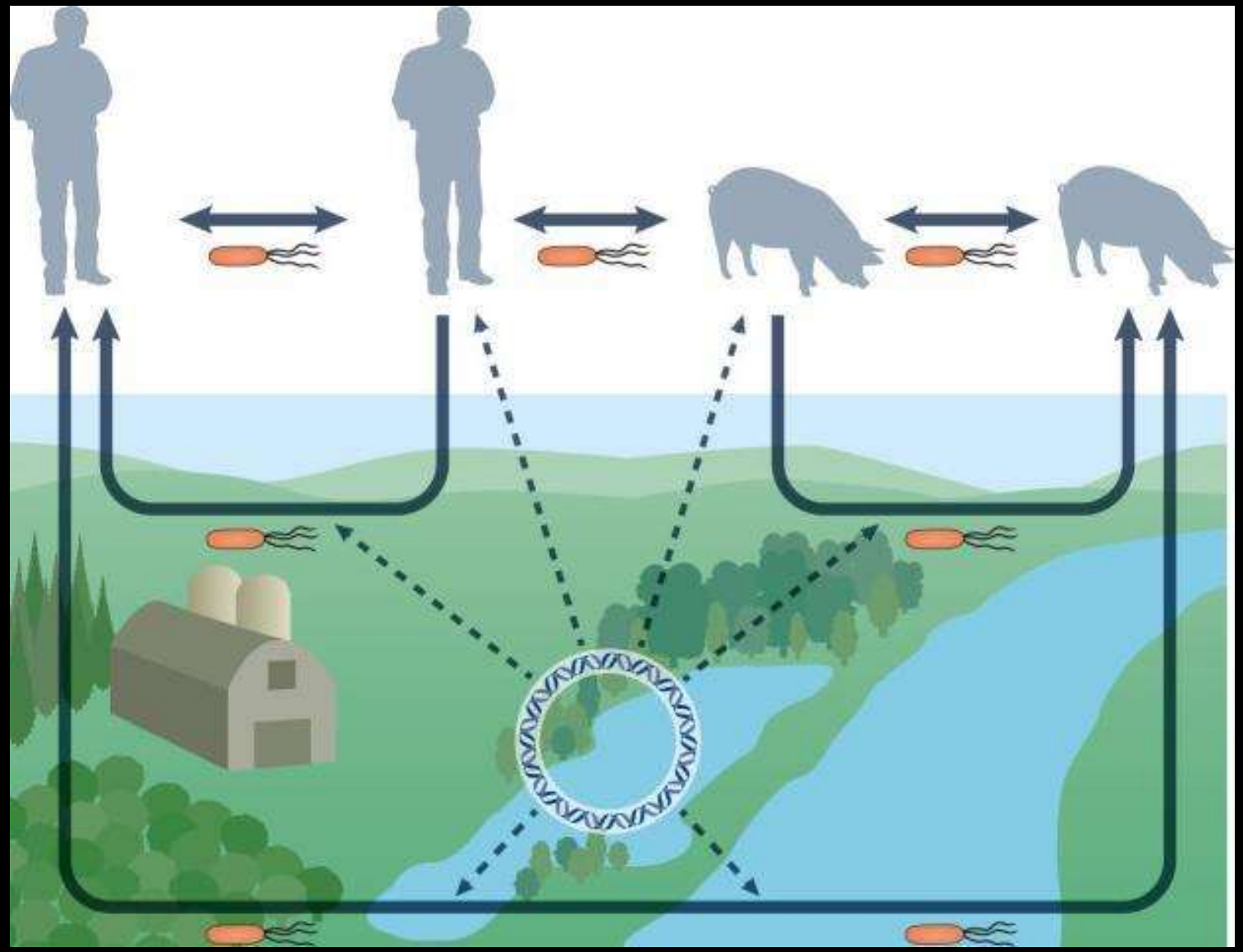
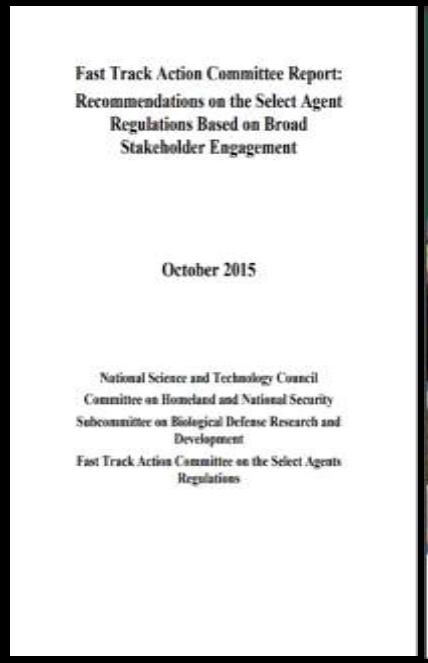
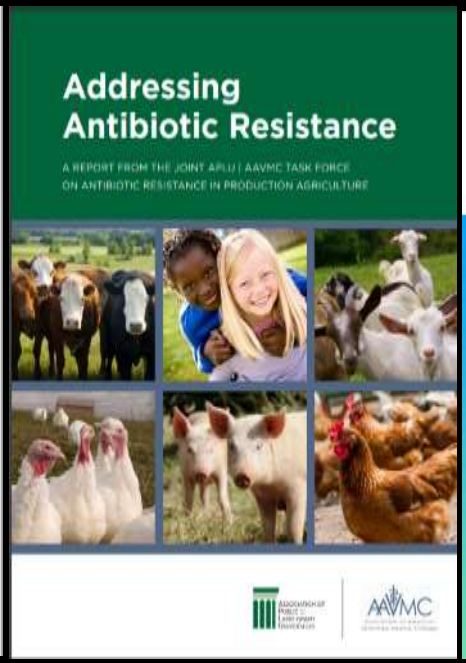
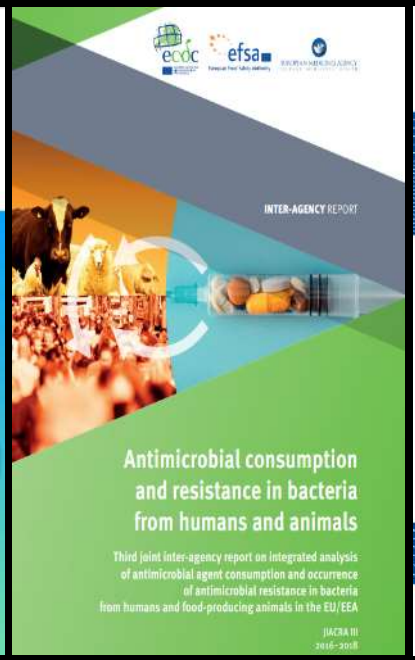


Fig. 3. From D.G.J. Larsson and C.F. Flach (2022) Nature Rev. Microbiol. 20, 261


Fast Track Action Committee Report:
Recommendations on the Select Agent Regulations Based on Broad Stakeholder Engagement
October 2015
National Science and Technology Council
Committee on Homeland and National Security
Subcommittee on Biological Defense Research and Development
Fast Track Action Committee on the Select Agents Regulations


Addressing Antibiotic Resistance
A REPORT FROM THE JOINT APLU | AAVMC TASK FORCE ON ANTIBIOTIC RESISTANCE IN PRODUCTION AGRICULTURE
AAVMC


NATIONAL QUALITY FORUM
National Quality Partners Playbook™:
ANTIBIOTIC STEWARDSHIP IN POST-ACUTE AND LONG-TERM CARE

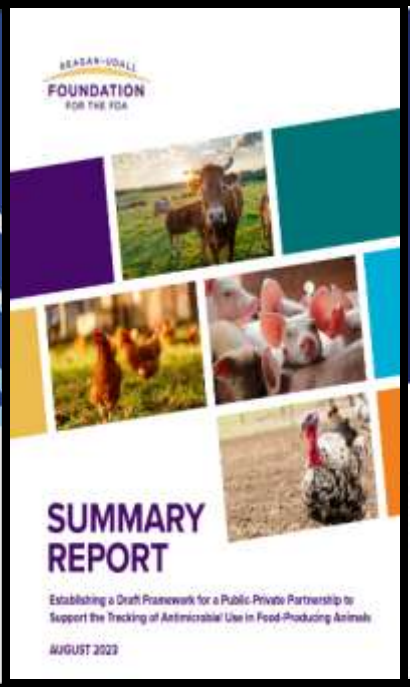

ecdc
efsa
INTER-AGENCY REPORT
Antimicrobial consumption and resistance in bacteria from humans and animals
Third joint inter-agency report on integrated analysis of antimicrobial agent consumption and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA
JIACRA III
2016–2018


Review on Antimicrobial Resistance
TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:
FINAL REPORT AND RECOMMENDATIONS
THE REVIEW ON ANTIMICROBIAL RESISTANCE
CHAIRED BY JIM O'NEILL


ANTIBACTERIAL AGENTS IN CLINICAL DEVELOPMENT
An analysis of the antibacterial clinical development pipeline, including tuberculosis
World Health Organization

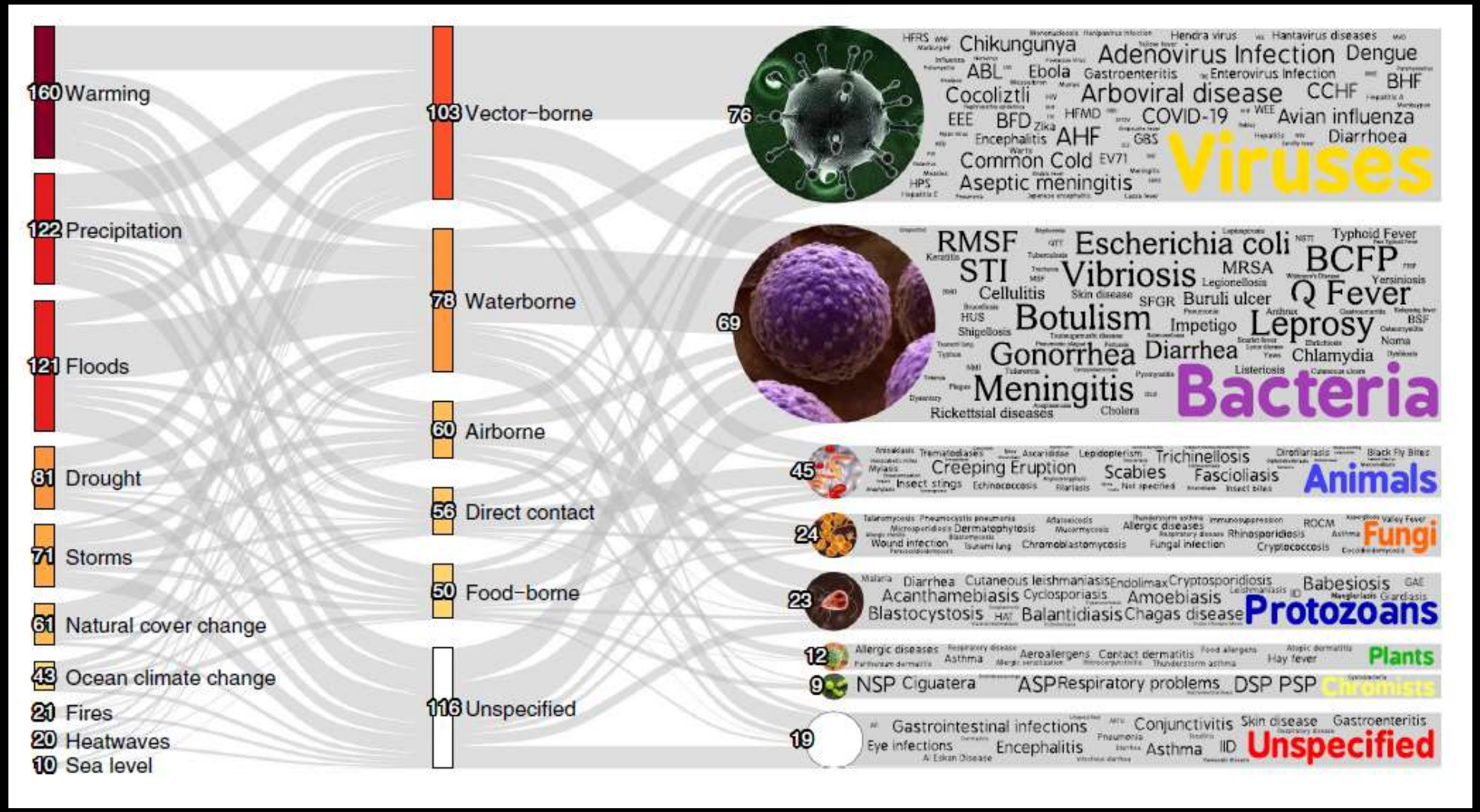

development dialogue paper
no.26 | december 2018
Antimicrobial resistance and sustainable development:
A planetary threat
but a financing orphan


WHO GUIDELINES ON USE OF MEDICALLY IMPORTANT ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS
World Health Organization


REAGAN-UDALL FOUNDATION FOR THE FDA
SUMMARY REPORT
Establishing a Draft Framework for a Public-Private Partnership to Support the Tracking of Antimicrobial Use in Food-Producing Animals
AUGUST 2023


SUPPORTING ANTIMICROBIAL STEWARDSHIP IN VETERINARY SETTINGS
Goals for Fiscal Years 2024-2028: Key Phase 3 and Phase 4 Actions
FDA CENTER FOR VETERINARY MEDICINE
September 2023
U.S. FOOD & DRUG ADMINISTRATION

Over Half of Known Human Pathogenic Diseases Can Be Aggravated By Climate Change



C. Mora et. Al. (2022) Nature Clim. Chan. 12, 869

Arizona Health Improvement Plan
Summary Document
2021-2025

ARIZONA ONE HEALTH TOOLKIT

ADHS

Vector-Borne & Zoonotic Disease: 5-Year Report 2018-2022

Maricopa County Public Health

one HEALTH

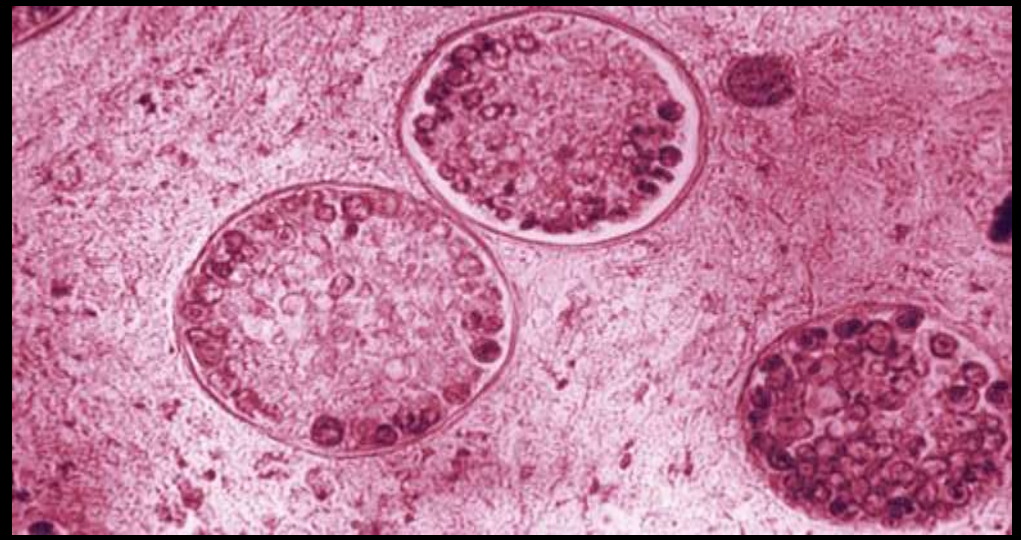
MARICOPA COUNTY

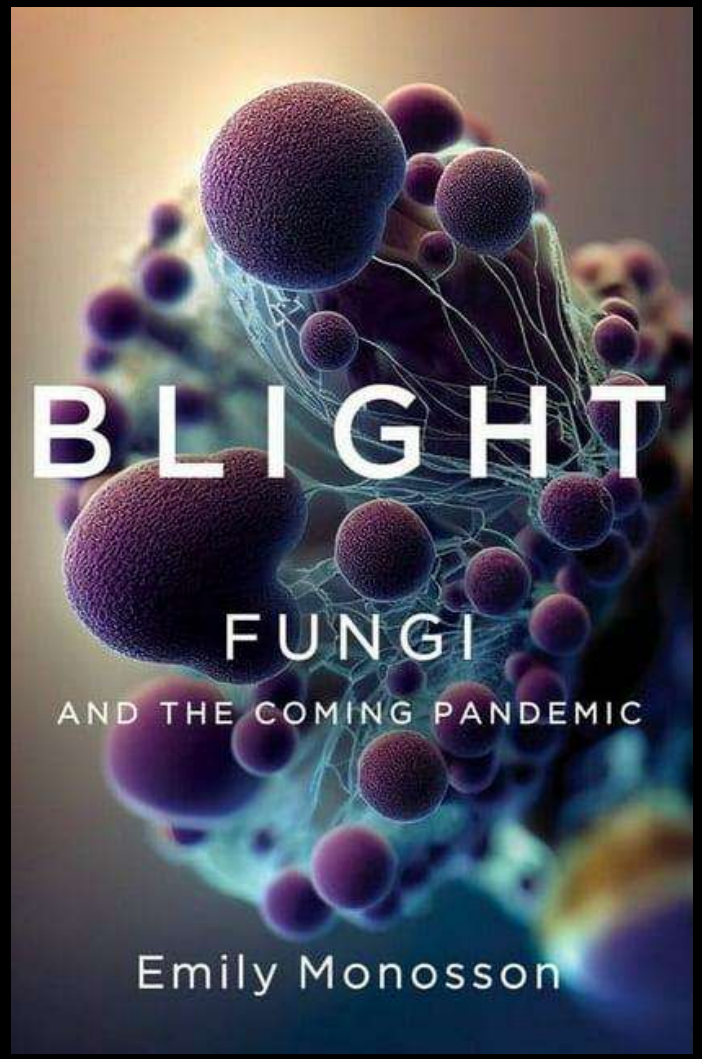
FIGHT the BITE!

Vector Borne Diseases Projected to Increase in Southern Arizona and Maricopa County

- Chagas disease
- chikungunya
- dengue
- Ehrlichiosis
- Lyme disease
- malaria
- Rocky Mountain Spotted Fever
- St. Louis Encephalitis
- West Nile virus
- Yellow Fever
- Zika


Understanding
Valley Fever:
A Must for
Dog
Owners
SALT RIVER
VETERINARY SPECIALISTS





J Fungi (Basel). 2023 Jun 30;9(7):720. doi: 10.3390/jof9070720.

Candida auris in Dog Ears

Anamika Yadav [1 2], Yue Wang [3], Kusum Jain [1 2], Vijay Amrit Raj Panwar [4], Hardeep Kaur [2], Vikas Kasana [1], Jianping Xu [3], Anuradha Chowdhary [1]

Affiliations + expand

PMID: 37504709 PMCID: PMC10381908 DOI: 10.3390/jof9070720

THE NEW PANDEMIC FUND AIMS TO:

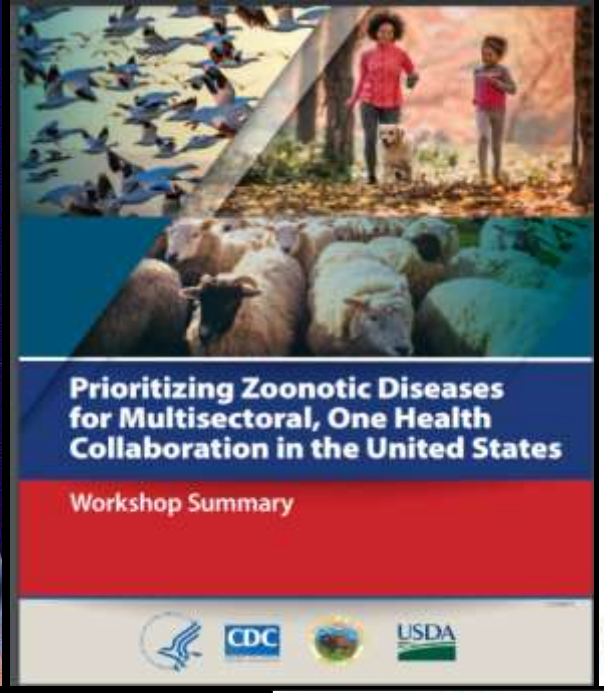
- *bring additional, dedicated resources*
- *incentivize countries to increase investments*
- *enhance coordination among partners*
- *serve as a platform for advocacy*

WORLD BANK GROUP

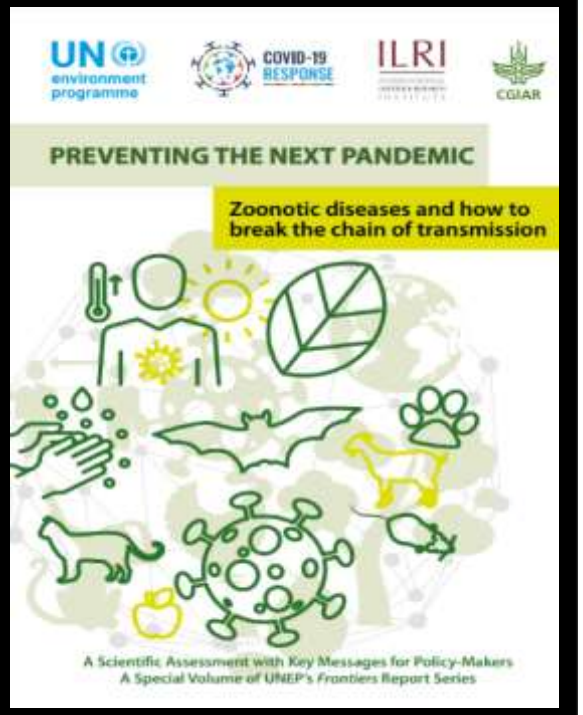
World Health Organization

- renewed focus and funding to strengthen global public health is necessary but not sufficient
- without adoption of One Health as a core principle in global biosecurity then laudable aspirations for human and planetary health will be undermined by:
  - continued cycles of emergent novel zoonotic EIDs
  - increased infectious disease threats to agricultural livestock and crops
  - food insecurity and depletion of non-renewable natural resources and other ecosystem disruption and prospect of food and water shortages
  - increased risks of socio – cultural – economic instabilities as triggers of conflict


NCEZID
2021
ACCOMPLISHMENTS
NATIONAL CENTER FOR
EMERGING AND ZOONOTIC
INFECTIOUS DISEASES
CDC


Prioritizing Zoonotic Diseases
for Multisectoral, One Health
Collaboration in the United States
Workshop Summary
CDC
USDA

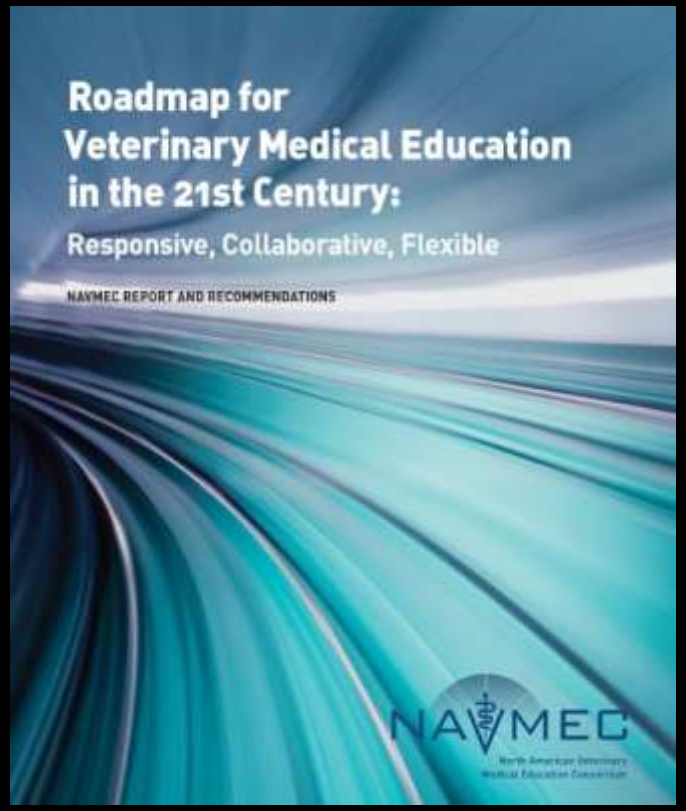

One Health
World Health Through Collaboration


UN environment programme
COVID-19 RESPONSE
ILRI
CGIAR
PREVENTING THE NEXT PANDEMIC
Zoonotic diseases and how to
break the chain of transmission
A Scientific Assessment with Key Messages for Policy-Makers
A Special Volume of UNEP's Frontiers Report Series


Food and Agriculture Organization of the United Nations
UN environment programme
World Health Organization
World Organisation for Animal Health
ONE HEALTH
JOINT PLAN OF ACTION
(2022-2026)
WORKING TOGETHER FOR
THE HEALTH OF HUMANS, ANIMALS,
PLANTS AND THE ENVIRONMENT

Precision Medicine and One Health: New Opportunities to Reverse the Historical Uncoupling of Human and Veterinary Medicine

- consumer expectations for advances in companion animal care and assimilation of precision medicine technologies from human medicine into veterinary practice
- major opportunities to leverage canine clinical trials as preclinical models to de-risk the current unsustainable cost of failure of investigational drugs in human trials
- one health: strengthening inter-dependencies between sustainable human, animal and environmental systems as a core element in future global biosecurity



MARS Veterinary Health

The Looming Shortage in Veterinary Professionals (August 2023)

- **2030**
  - **projected shortage of 24,000 companion-animal veterinarians**
  - **even larger shortfall in credentialed veterinary technicians**

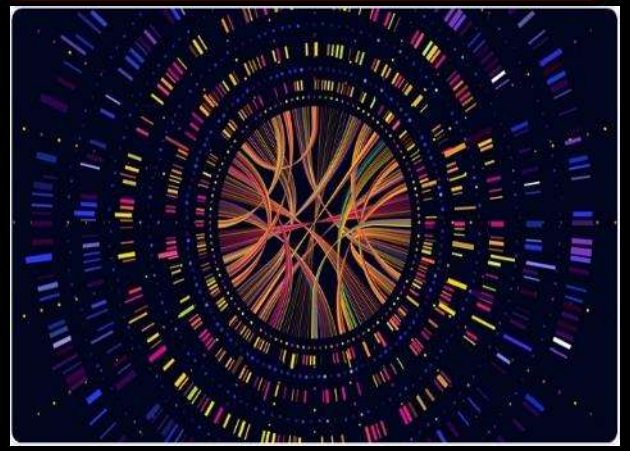
Precision Health and One Health: Technology Acceleration and Implications for Professional Training and Competencies

- shared challenges between human and veterinary medicine
- contemporary curricula in both medical and veterinary schools not keeping pace with the breadth and complexity of technological innovation
- intensifying continuing education needs to sustain professional competencies
- burnout and concern over replacement of professional skills by automated ML/AI processes/decisions

Precision Health and One Health: Technology Acceleration and Implications for Professional Training and Competencies

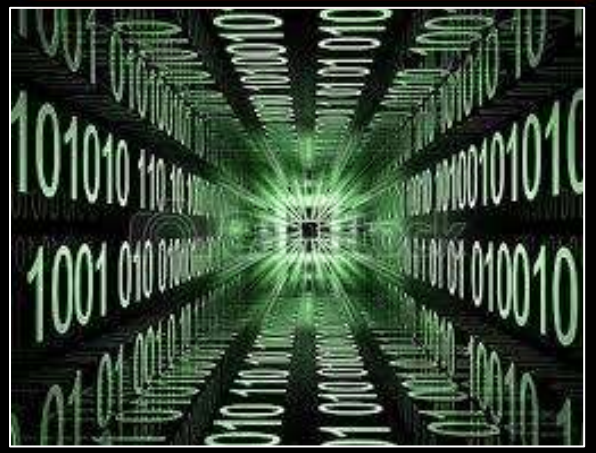
- additional challenges in veterinary education
  - looming shortage of trained professionals (and credentialed technicians)
  - demographic imbalance between companion animal and livestock practitioners
  - inadequate role models and incentives for non-clinical careers in biomedical research, biotechnology industry and global biosecurity
  - rising educational debt and declining ROI

multiOmics and precision health



remote health monitoring

Big Data

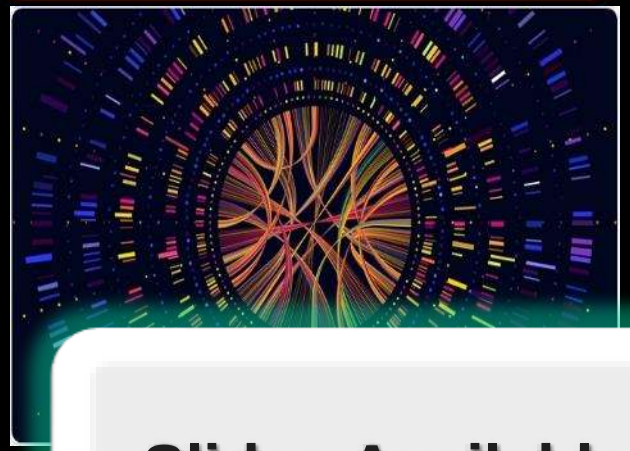


improved translation

one health

the future veterinarian

multiOmics and precision health



remote health monitoring

Big Data

Slides Available @ http://casi.asu.edu/presentations

improved translation

one health

the future veterinarian