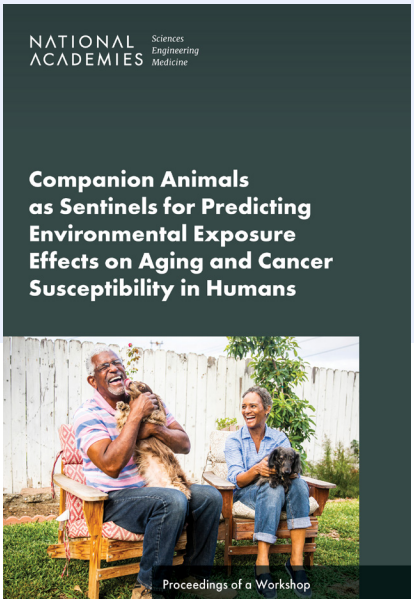
NATIONAL ACADEMIES Sciences Engineering Medicine

Proceedings of a Workshop
Highlights

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



The National Academies of Sciences, Engineering, and Medicine hosted a hybrid workshop, The Role of Companion Animals as Sentinels for Predicting Environmental Exposure Effects on Aging and Cancer Susceptibility in Humans, on December 1–3, 2021, in Washington, DC. The webcast and workshop presentations are available online.[1] Presentations and panel discussions covered the current state of the science and pathways for accelerating this novel translational research approach to advance human health.

The One Health movement aims to focus attention and resources on areas of overlap among environmental health, human health, and animal health, explained Frank A. von Hippel (University of Arizona). Michael Blackwell (University of Tennessee, Knoxville) emphasized the interconnections between human health outcomes and the health of animals and the environment. Companion animals and humans share many environmental exposures and are susceptible to many of the same age-related diseases, including cancer, explained Peter Rabinowitz (University of Washington). Companion animals have the potential to provide new insights that are complementary to traditional research approaches and have "untapped potential" for detecting environmental carcinogens that may help improve human cancer prevention, he added.

THE RATIONALE FOR ANIMALS AS SENTINELS OF ENVIRONMENTAL EXPOSURES

The benefits of using dogs and cats as sentinels of harmful environmental exposures has been demonstrated through several

[1] See https://www.nationalacademies.org/event/12-01-2021/the-role-of-companion-animals-as-sentinels-for-predicting-environmental-exposure-effects-on-aging-and-cancer-susceptibility-in-humans-a-workshop (accessed August 26, 2022).

public health emergencies over the last century, said Kurunthachalam Kannan (New York University). For example, industrial mercury dumping in the fishing village of Minamata, Japan, contaminated the local fish supply; local cats, who ate leftover fish, displayed "dancing cat fever" years before the neurological symptoms of mercury poisoning became evident in people, he explained. Cats have many disease syndromes that closely parallel those in humans, including cat versions of severe acute respiratory syndrome, acquired immunodeficiency syndrome, and other viral diseases, as well as many respiratory and endocrine disorders, said Jan Dye (Environmental Protection Agency [EPA]). Cats' and dogs' condensed life spans, indoor lifestyles, veterinary records, and fully sequenced genomes enable their use as sentinels to investigate human disease syndromes in terms of environmental exposures, she said.

Dogs are effective sentinels for air pollution, said Caleb Finch (University of Southern California), citing postmortem studies that compared dogs in Mexico City to those in coastal cities with far less pollution. The Mexico City dogs had significant neuron loss in the brain stem and their myocardium contained silica-like crystals, he explained. In addition, many studies have demonstrated the utility of dogs as sentinels for the reproductive effects of environmental contaminants, explained Richard Lea (University of Nottingham). He noted that dog testes and ovaries, which are disposed of in large quantities following spay/neutering procedures, are a valuable resource that can be used both to screen for environmental contaminants and to study the connection of these agents to specific pathologies.

Shared exposures are the norm in the 40 percent of U.S. homes that include pet dogs, said Audrey Ruple (Virginia Tech). Not only do pets share a common living space with humans, their behavioral patterns resemble those of toddlers, including mouthing objects and contact with the ground, noted Kannan. Dogs are also a good model species for genetics, said Adam Boyko (Cornell University). There are hundreds of dog breeds, and they have greater genetic differentiation than within human populations, with larger ranges of phenotypic diversity, including a 50-fold difference in body size that correlates with a 2-fold difference in aging rate, he explained. This provides a useful model for genetic association studies and for mapping the mutations that underlie specific phenotypes, said Boyko.

COMPANION ANIMALS AS SENTINELS FOR CANCERS LINKED TO ENVIRONMENTAL EXPOSURE

Gary Ellison (National Institute of Environmental Health Sciences [NIEHS]) explained that exposures to environmental carcinogens are correlated with increased risk of different cancers (e.g., pesticide exposure is linked to lung cancer and radiation exposure to stomach cancer). However, he added that documenting exposure to environmental carcinogens is complex due to long latency, timing of exposure, epigenetic changes, and variation among individuals in genetic risk factors and windows of susceptibility. Ruple emphasized that decades may elapse between exposure and onset of illness, making it difficult to identify environmental carcinogens in humans. In contrast, dogs have shorter life spans and their cancers have much shorter latency periods. Given the lifelong immersion of companion animals in the human environment, data collected on their exposures and health outcomes have the potential to provide new insights into environmentally-induced diseases that can complement traditional laboratory, clinical, and public health studies, added Rabinowitz. Matthew Breen (North Carolina State University) added that the 7-fold difference in longevity between humans and dogs allows scientists to "harness the impacts of environmental influences on our pet dogs living in our environment, but over a much shorter period of time."

Cancer etiology involves both genetic and environmental factors, Ruple said, so the best sentinels for carcinogens would be similar to humans in terms of both genetics and exposure. Dogs share about 650 million base pairs of ancestral DNA sequence with humans, and dog orthologous genes are more similar to humans than are the same genes from mice, she added. Ned Sharpless (National Cancer Institute [NCI]) said that companion animals could help identify the links between environmental agents and cancer. Dogs and humans not

only share the same environment but also possess many similarities in genetics, physiology, tumorigenesis, and cancer progression, he explained (see Figure).

A fundamental question, noted Rod Page (Colorado State University) and Amy LeBlanc (NCI), is how to validate a canine model as a sentinel. A new body of epidemiological evidence from companion animals can complement—not replace—the body of epidemiological evidence from humans and the experimental evidence from animal exposure studies and in vitro work, noted Rabinowitz. For example, Dye described how PFAS exposures in humans have been linked to kidney and testicular cancer, abnormal thyroid hormone levels, pregnancy-induced hypertension, and high cholesterol with associated liver disease. When the researchers examined cats with liver disease, feline hyperthyroidism, respiratory effusions, or kidney disease, they found elevated levels of PFAS compounds in the sick cats compared to the healthy cats, she said. Noting that more than 50 percent of U.S. households have one or more pets, Dye challenged investigators to take collaborative, transdisciplinary approaches to address data gaps in this untapped population and take advantage of newer technologies to identify new associations between exposures and health outcomes.

Dogs are good models for studying osteosarcoma with diagnoses in more than 10,000 dogs each year, LeBlanc added. Pediatric and canine osteosarcomas look strikingly

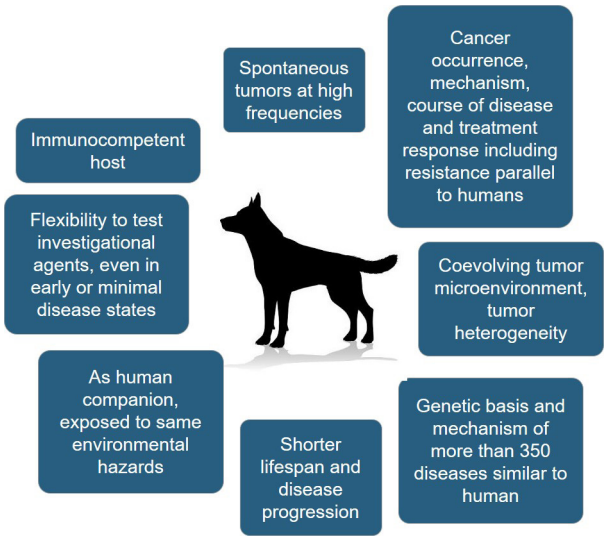


FIGURE Dogs can serve as a useful model for human cancers.
SOURCES: Sharpless presentation, December 1, 2021. Adapted from Bujak et al., 2018.

similar at histopathological, molecular, and clinical levels, including the tendency of the tumor to metastasize to the lung, she explained. LeBlanc and colleagues are working to define a genomic signature for canine osteosarcoma for integration with human osteosarcoma data to identify new druggable targets for preclinical work, with the ultimate goal of benefiting both canine and human patients. Unlike humans who enroll in clinical trials of novel therapies, dogs with osteosarcoma provide a source of treatment-naïve tissue, enabling the development of a biospecimen repository with primary tumors, matched normal tissue, blood, and other samples, she said.

Sharpless added that NCI is also interested in studying cancer immunotherapies in clinical trials for companion dogs with naturally occurring tumors to help advance treatments for both animals and humans, noting that NCI also created a large Integrated Canine Data Commons (ICDC) in its Cancer Research Data Commons, which maintains data from clinical trials for dogs with cancer. The ICDC contains a wide variety of genetic, clinical, immunological, and imaging sets in a cloud-based resource with computational tools, said LeBlanc, who encouraged its use for sharing and analyzing data.

COMPANION ANIMALS AS SENTINELS FOR AGE-RELATED DISEASES LINKED TO ENVIRONMENTAL EXPOSURES

Finch explained that the "gero-exposome"—gene–environment interactions that produce aging phenotypes—applies equally to domestic animals as humans. Finch raised the possibility of a connection between secondhand smoke and dementia in humans, which could be investigated in companion dogs because canine brain amyloid Aβ42, which correlates with cognitive dysfunction, increases with aging. Finch added that, unlike rodents, dogs naturally accumulate plaques and tangles with aging, produce the same amyloid peptide as humans, and have the same distribution of Alzheimer's-like pathology in the brain.

Several workshop speakers described examples of current studies that have examined the role of environmental exposures in aging and cancer in companion animals (see Box).

BOX

Examples of Studies in Progress Examining the Role of Environmental Exposures in Aging and Cancer Described by Workshop Speakers

Golden Retriever Lifetime Study (Rod Page, Colorado State University): The Golden Retriever Lifetime Study is an observational study that seeks to produce valuable information on canine cancer, including incidence and risk factors, both genetic and environmental. Additional goals include developing new early detection technologies, biomarkers, and prevention strategies, and follow-up studies that may eventually test interventions. Diagnosis of one of the four types of cancer most common in golden retrievers was chosen as a primary endpoint. Annual data collection includes questionnaires for both owners and veterinarians as well as collection of biospecimens.

Dog Aging Project (Daniel Promislow, University of Washington): The Dog Aging Project (DAP) is a longitudinal study focused on the biological and environmental determinants of healthy aging. To generate longitudinal data capable of hypothesis testing, owners complete annual online surveys. In addition to the health and life experience survey, these include behavioral, cognitive, environmental, and end-of-life surveys. The DAP is an open science project and all data will be made publicly available.

Combined Clinical-Environmental Studies on the Domestic Dog as a Sentinel Species for Environmental Influence Associated with Bladder and Other Cancers (Matthew Breen, North Carolina State University): Breen and colleagues have begun enrolling dogs in combined clinical–environmental studies, the first of which is looking for environmental associations with bladder cancer in dogs, who are typically diagnosed at age 6 or older. The researchers developed a "liquid biopsy" that enabled them to detect very early bladder cancer based on gene signatures in the urine, allowing analysis of the earliest genetic changes. Working with the American Kennel Club (AKC), they recruited owners of 2,000 dogs aged 6–12 years from seven breeds with a high predisposition for bladder cancer to examine shared exposures. Their first project, using silicone wrist bands and matched urine to investigate shared exposures, has revealed "striking … similarities between exposures of our dogs and ourselves," said Breen.

Silicone Wristbands to Monitor Exposures (Heather Stapleton, Duke University): In collaboration with Breen, Stapleton has been testing silicone wristbands as wearable samplers. These wristbands are made of polydimethylsiloxane, which can be used to measure ambient exposure to a variety of compounds, particularly those inhaled or absorbed through the skin. Their research found a strong correlation between exposures measured on human wristbands and on companion dog tags for a range of chemicals, including legacy polychlorinated biphenyls, a novel flame retardant, pesticides, and a component of flea/tick treatments. Silicone tags have also been used to measure exposures to endocrine-disrupting compounds in cats.

Embark (Adam Boyko, Cornell University): Noting that direct-to-consumer genetic testing of humans has built data sets on the order of tens of millions of individuals, Boyko developed a similar model for dogs. Embark began in 2015 and now has more than 900,000 dogs in its database, each of which has been genotyped at more than 230,000 markers—one of the biggest dog genetic databases in the world.

STATE OF THE SCIENCE FOR BIOMARKERS OF EXPOSURE AND THE USE OF BIOSENSORS

Both humans and their animal companions experience a broad range of physical and chemical exposures, but to affect health, an exposure must be converted to a biological signal inside the body, said Gary Miller (Columbia University). Capturing the breadth of these exposures will require a suite of tools, from wearable devices and biospecimens to computational imaging and satellites. The disease-related metabolic similarities between species as evolutionarily distant as worms and people suggest that the potential for cross-species metabolome analysis in companion dogs and humans is very strong, said Miller. A novel microneedle patch that can sample interstitial fluid from skin without a blood draw may be helpful for sampling pets at home. Miller cautioned that developmental windows matter, so knowing which stages of the human and animal life spans were co-exposed when doing paired cross-species studies is important.

Environmental exposures show dramatic variation in type, timing, and dose across populations, time, and space, and therefore require a variety of tools for their detection and analysis, added Yuxia Cui (NIEHS). NIEHS sponsors the development and refinement of a variety of wearable and field-deployable tools for characterizing personal exposures to air pollution and for monitoring physiology, she said. Although these are primarily for use in humans, they can be adapted for companion animals, Cui explained. She added that NIEHS-supported sensor research includes the development of hardware, software, miniaturization, improvements to battery life, and laboratory and field-testing to improve accuracy and reliability.

PARTICIPANT REFLECTIONS AND LOOKING AHEAD

Standardized data models are needed for canine population studies, said Anne Thessen (University of Colorado). Page and Promislow noted that electronic medical record (EMR) systems in veterinary medicine are extremely variable and proprietary, and new systems would likely need to be built to make animal and human EMRs compatible. NCI's ICDC may prove a useful foundation, said Page. Although the ICDC was initially conceived as a repository of canine cancer genome data, it has broadened to include various types of data related to cancer development that have a rationale for comparison to humans, and this offers a huge opportunity for inclusion of environmental exposures, added LeBlanc. The ICDC contains data on bladder cancer, osteosarcoma, and glioma, including genomics, transcriptomics, and imaging, said LeBlanc.

One research goal is to overlay human and canine EMRs with environmental exposure maps and geo databases, such as those being developed by NIEHS, said Breen and James DeGregori (University of Colorado). This is expensive and requires coordination of human clinicians, veterinary medical professionals, and data scientists, noted Breen. Promislow suggested bringing together leaders of prospective studies for humans and pets in a roundtable to discuss strategies for collaborative work.

Boyko suggested paired genome-wide association studies of dogs and their owners. Rena Jones (NCI) encouraged researchers to propose ancillary pet studies for human studies that are recruiting new cohorts, such as the intramural NCI Connect for Cancer Prevention study, which includes infrastructure for geographic information system (GIS) mapping and location-based exposure assessments, with complete residence histories and drinking water intake data. She expressed the need to gather more data on disadvantaged populations, which tend to be underrepresented in many cancer study cohorts. Linda Birnbaum (NIEHS, emeritus) discussed the possibility that the NIEHS and the NCI might provide supplemental funding to add pet biomonitoring and outcome data to existing human longitudinal studies.

Danielle Carlin (NIEHS) suggested developing studies that collect biospecimens from humans and pets simultaneously (e.g., through existing mobile vet clinics). Promislow said that integrating pet research with human research might motivate owners to engage more in this kind of work. Jones encouraged researchers to leverage existing, geographically-linked exposure data as an additional resource to supplement the collection of environmental data and biospecimens, noting that "those data exist and have been mined and cleaned and resourced for lots of different purposes" and could

function as a hazard identification tool, particularly for investigating new exposures.

Marta Castelhano (Cornell University) is integrating data from human and dog biobanks, with bioinformaticians working to standardize the platforms; in order to encourage specimen sharing and collaboration, she emphasized that biobanks need infrastructure support, including HEPA-filtered air in sample preparation and freezer rooms; cryogenic homogenization; and 24-hour monitoring systems for freezers; as well as risk management plans to avoid loss of collections during a natural disaster. She added that a national, centralized environmental specimen banking initiative for human and sentinel species would be ideal.

Marcia Haigis (Harvard University) and Elaine Ostrander (National Human Genome Research Institute) emphasized the need to make the large canine omics data being accumulated freely accessible to investigators so they can use informatics approaches to generate hypotheses for cancer mechanisms. Promislow envisioned the creation of a DNA Data Commons for dogs, where all studies collecting DNA data would share information. Sharing DNA data presents challenges regarding consent, privacy, and consistency, but there may be ways to harmonize it, he said.

"We should not have to reinvent the wheel," said Page, suggesting the expansion of NCI's ICDC to contain exposure data and other types of data from studies on a broader scale across species, with the vision of a common exposure and genomic analysis. Active work to promote data accuracy, collation, integration, curation, and accessibility is needed, and that will require targeted funding, said Breen. Nicole Deziel (Yale University) noted many opportunities for researchers to tap into existing cohorts, both human and animal. Carlin added that the research community needs to develop ways to collaborate with and access the data from Mars Petcare and other large commercial data sources, as well as diverse federally funded data sources, such as the Multi-Ethnic Study of Atherosclerosis and the National Health and Nutrition Examination Survey, which collects data on water and dust samples and has access to Social Security and Medicaid data. GIS data could be leveraged for companion animal studies, she added.

The veterinary primary care community plays a critical role in helping to gather data for companion animal studies, noted Promislow, but these veterinarians often do not have the bandwidth or motivation to participate in studies. This presents a challenge for researchers, who need to persuade the veterinarians that it is worth their time to participate in a scientific study and to help them guide their clients through informed decision making about their own participation, he explained.

Chad Johannes (Iowa State University) discussed the need for public health training for clinicians and veterinarians. Ryan suggested encouraging veterinary students to take public health courses and, in some cases, to complete dual DVM and MPH degrees. DVM programs could be tailored to include an extra year to accommodate this training, said Joseph Wakshlag (Cornell University), adding that public health is also relevant to oncology, internal medicine, and nutrition. Greater support for teaching comparative medicine and research is also needed in medical schools, said Carlin. Companion animal studies can be used to train interdisciplinary personnel in public health, medical, and veterinary schools, as well as professionals in the social sciences who will be needed to bridge cultures and work closely with participants in community-based participatory research, added William Farland (Colorado State University, emeritus).

Ellison noted that companion animal research lends itself well to citizen science approaches and that NIEHS now requires community engagement with most funding opportunities; for example, to capture data on exposures, citizen scientists collect biospecimens like toenails, hair, and teeth from their pets. Miller added that the exposure–disease connection needs to be better communicated to the public when sharing results.

CHALLENGES IN USING COMPANION ANIMALS AS SENTINELS

Ruple noted several limitations to the use of animals as sentinels of environmental exposures. Demographic information is an important denominator for some of this research and is lacking among animal populations,

including purebred dogs, mixed breeds, and cats. There is no nationwide census of dogs in the United States, no dog cancer registry, and the burden of cancers in dogs is not captured by veterinary records that list the cause of death as euthanasia, which makes it difficult to assess the actual incidence of cancers in dogs, she said. The AKC, the American Veterinary Medical Association, and industry can help obtain this information, said Farland, and adding a question about pets to the 2030 Census would also be useful. One approach to improving the denominator, suggested Promislow, would be to have a team of human demographers and geospatial scientists work with the databases from Mars Petcare's veterinary hospitals and clinics to develop models that could derive estimates of the denominators based on existing information such as breed, age, and size. Boyko noted other limitations of using dogs as models for humans, including incomplete age data and differences in the degrees to which stature, reproductive history, smoking, and inbreeding influence health outcomes in the two species.

Unlike humans, only about 3 percent of pets have health insurance, which influences the choice of treatment, said Johannes. The number of dogs with cancer is often underestimated because they many never receive a definitive diagnosis or even see the vet because pet owners cannot afford the tests and treatments, he explained. Sample collection is expensive, making it a challenge to fund, particularly for larger-scale studies, said Promislow, and for large studies, the cost can be prohibitive. Carlin added that the research community needs to develop new funding strategies.

Embedding ethical considerations into research strengthens study design and validity, said Lisa Moses (Harvard Medical School), who is one of two ethicists consulting on the DAP. Moses highlighted three ethical issues that are relevant for companion animal studies: (1) informed consent does not exist for animals, (2) pets are not protected by laboratory animal research regulations, and (3) payment or other compensation for enrollment can be coercive with pet subjects, due to inequities in access to veterinary care in the United States. While citizen science has tremendous potential to democratize science, it carries its own ethical concerns, added Moses. It is essential to incorporate the principles of reciprocity, where participants benefit from their involvement, and reflexivity, where investigators examine the influence of their own beliefs and practices on the research, she added. Other useful strategies include diversifying participants, which improves data generalizability, and building in learning objectives to enhance participants' scientific literacy, she said. It is critically important to gain cultural competencies when engaging different populations in studies, added Blackwell, as historical experiences, such as the Tuskegee Syphilis Study, have molded perceptions of research within these communities. Often the only connection they have with outsiders around their pets is through animal control, which translates as policing, so we need to be attentive to those perceptions, said Blackwell. Research with a long timeline can be challenging, said Blackwell, but underserved and underresourced communities may require a long period of engagement to establish trust with researchers.

Community-engaged research is essential to avoid perpetuating inequities or discriminating against disadvantaged populations, and ideally takes the form of community-based participatory research, said von Hippel. For example, when working with Indigenous populations, it is essential to obtain consent from the community and tribe in addition to the dog's owner, and the community should benefit from the work, he said. The tribe he works with owns von Hippel's data and he reports results to them before publishing; "I think that protection for the tribe is critical so they feel confident that they are not being exploited and that the work is really to benefit the community, rather than just researchers coming in, doing their work, and never hearing from them again, which is the way it used to be that was so problematic," he added.

PRIORITIZING STUDIES TO MAXIMIZE IMPACT

Given the broad range of measurable exposures and finite resources, prioritizing study questions will be crucial, said Promislow, who noted that studies vary in their aims. Stapleton advocated for a focus on ambient measurements that are cumulative over time, in an

exposomic framework, while also paying careful attention to the diet and microbiome. Ryan highlighted changes to the microbiota and immune evasion by tumors as two potential markers of the effects of chemical mixtures. The key value of these longitudinal studies is their tissue and data banks, said Wendy Shelton (Virtual Beast/Colorado State University), and it will be important for future researchers with fresh ideas and technologies to be able to access these resources. Wakshlag said that given the capability to measure "just about anything" and the ongoing longitudinal dog cohorts, now is the time to assemble expert panels to identify the important exposures to study. "Where are sentinel animals poised to have the most impact?" asked Carlin, suggesting studies on physical health, exercise, and obesity, as well as mental, emotional, and social health and well-being.

WORKSHOP WRAP UP

There is a need to better understand exposure and the environment that companion animals live in, and this requires augmenting the information that veterinarians typically collect, said Farland, who reviewed methods covered at the meeting, including GIS, proximity to sources, and both active and passive sampling. He suggested leveraging existing environmental data and exposure information collected by the NIEHS, the EPA, and state and local health departments. Plenty of specimens have already been carefully collected and stored, noted Farland; the question is how to make the best use of these specimens and surmount institutional barriers to making them available for study.

Animals can be effective sentinels because of greater susceptibility, greater exposure, and shorter latency for adverse effects of environmental factors, explained Birnbaum. Furthermore, she added that domesticated dogs are exposed to some of the same environmental selection pressures as people, and dog orthologous genes more closely resemble those of humans than do rodent genes. To refine these studies, "we need to define what we mean by environment," said Birnbaum, noting that in this workshop, "environment" seemed to include all nongenetic factors while incorporating windows of susceptibility, effects of early life exposure, transgenerational effects, mixtures, interactions, and cumulative exposures. The genome, epigenome, microbiome, and metabolome act as both targets and mediators of environmental exposures, she explained. Our companion animals can inform us not only about cancer and aging but also many other human health conditions, said Birnbaum, including those involving the immune system and the microbiome.

FOR MORE INFORMATION

This Workshop Highlights was prepared by **Ruth Cooper, Lori Brenig,** and **Sharyl Nass** as a factual summary of what occurred at the workshop. The statements made are those of the rapporteurs or individual workshop participants and do not necessarily represent the views of all workshop participants, the planning committee, or the National Academies of Sciences, Engineering, and Medicine.

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Additional information regarding the workshop and the poster session is available online at https://www.nationalacademies.org/our-work/the-role-of-companion-animals-as-sentinels-for-predicting-environmental-exposure-effects-on-aging-and-cancer-susceptibility-in-humans-a-workshop.

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