

# A New Medical Research Model: Ethically and Responsibly Advancing Health for Humans and Animals

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## Abstract

With the increasing use of genomics, computational analytics, emerging technologies, and personalized medicine, the possibility of a new research model is emerging. Using the clues from thousands of species living on our planet, scientists from many disciplines (medicine, veterinary medicine, wildlife) must collaborate, prioritize, and strategize on how to address causes of health and disease. Such clues should guide disease prevention, as well as the development of innovative, efficacious, and gentler therapies. Geographic and language barriers must be broken down, and scientists—even within a single academic, corporate, or government research site—must be vigilant in seeking the help of nonmedical disciplines of colleagues from whence answers might come. The public will become more interested in and demanding of such a model, desiring that all family members (humans and animals) have an opportunity for a long and healthy life. Above all, such activities will be humanely conducted with outcomes having the greatest chance for success.

## INTRODUCTION

Animals used in research have contributed mightily to the advancement of human health. There have also been egregious uses of animals in pain, physiological, and psychological studies; cosmetic testing; and teaching programs. Some animal models have provided little information for treating disorders in humans, and research results from animals housed in facilities that fail to reflect natural environments (and variables) often yield results that cannot be translated to other species or environments. This review provides a historical overview of the use of animals in research, describes some of the limitations associated with the current medical research model, and proposes a new model that provides opportunities for breakthrough discoveries with a higher probability of preventing disease and developing gentler therapies for both animals and people.

## HISTORY: ANIMALS AND RESEARCH

René Descartes (1596–1650) is often referred to as the Father of Physiology and was also recognized for devising analytical geometry (1). As a scientist, Descartes stated that both a man and a beast might have similar thoughts. However, he has also been associated with the concept that animals withdraw from nocuous stimulus not because they feel pain but because of mere automata (machinelike withdrawal following a stimulus). Although it is unclear if he truly held this belief, Cartesians who came after Descartes did believe that the animal mind was wholly separate from the corporeal body and that animals therefore may lack consciousness and the ability to feel pain (2).

Although some scientists throughout history may have considered animals to be incapable of suffering, many animal advocates emerged who did not share this belief. The Animal Defense and Anti-Vivisection Society, established in England in 1903 by Lizzy Lind af Hageby (a Swedish feminist) and Nina Douglas-Hamilton, Duchess of Hamilton, strongly opposed vivisection on conscious animals (3). The society came to widespread attention during the Brown Dog affair (1903–1910), which was triggered by allegations that William Bayliss of the Department of Physiology at the University College London had performed a dissection on a conscious and struggling brown dog before an audience of medical students. Bayliss was an esteemed scientist who, along with Ernest Starling, discovered the first example of a hormone—a chemical substance that stimulates the secretion of pancreatic enzymes (4). Bayliss and Starling found this substance in dogs and coined the term hormone, providing scientific results that led to the advancement of endocrinology for both humans and animals. Although well known for his discoveries, Bayliss also became notorious because of allegations of animal abuse, leading to the establishment of a Royal Commission in 1906 to investigate the use of animals in experimentation. Critics thought the commission was stacked with those favoring few restrictions for animal experimentation (5). Similar criticisms continue to be expressed today by citizens who worry that scientists might be incapable of self-regulating and continue to place animals at risk for suffering in the name of academic progress. Such concern exists even when institutional animal care and use committees provide oversight for academic research and/or when federal agencies inspect research facilities that use animals in their programs. Additionally, private funding agencies have noted considerable variability among institutions in how research protocols are developed and approved by oversight bodies, as well as how animal comfort is, or is not, considered.

### The Animal Welfare Act in the United States

The Animal Welfare Act (AWA) was signed into law in 1966. The AWA requires that minimum standards of care and treatment be provided for certain animals for commercial sale, used in research, transported commercially, or exhibited to the public. The US Department of Agriculture's

Animal and Plant Health Inspection Service enforces the AWA and its standards and regulations. Rodents and birds—which make up approximately 95% of nonhuman animals used in laboratory research—are not covered under the AWA, something of concern to many animal advocates. Farm animals used in research are also excluded from the AWA. Excluded animals, however, often receive some oversight through the National Institutes of Health, the Association for Assessment and Accreditation of Laboratory Animal Care, and local institutional animal care and use committees (6). Animal advocates question why the AWA does not protect all animals used in research. They also express concern about the redundancy in the use of animals, questioning whether researchers are truly familiar with research studies and findings from other countries, or potential collaborations even within their own academic institution, prior to conducting research that includes animals.

Bernard E. Rollin, bioethicist and Distinguished Professor at Colorado State University, has been a longtime advocate for federal legislation that assures some minimal concern on the part of researchers for the welfare of laboratory animals (7). He argues that animal research may be both a scientific necessity and a moral issue on the basis of how such research is conducted. In 1982, he found only two references at the Library of Congress during a literature search for “analgesia for laboratory animals.” Because of his work, and the work of others, many researchers have become far more aware of controlling pain in animal subjects; preventing animal suffering; and promoting animal telos (enrichment) to provide animals with wellness, welfare, and well-being. Not only is this the moral thing to do, but it is an essential strategy to ensure valid research results and public acceptance for using animals in research studies. Although progress has been made in controlling pain, approved pain medications for most farm animals are lacking, suggesting that research is also needed to ensure drugs are developed that can be used to control pain both in animal research and for use in routine veterinary medicine.

### International Association for the Study of Pain (IASP) Guidelines

The IASP calls for national and regional guidelines addressing humane care and use of laboratory animals to ensure all research performed on live vertebrate animals will be done humanely (8). Authors must verify that they have adhered to such guidelines when submitting manuscripts for publication to *Pain* and when submitting materials for presentation at the biennial World Congress on Pain. Because animals are unable to communicate verbally or give informed consent, the burden upon each researcher is high to provide optimal animal welfare. According to the World Organization for Animal Health, an animal is in a good state of welfare (as indicated by scientific evidence) if it is healthy, comfortable, well-nourished, safe, and able to express innate behavior, and if it is not suffering from unpleasant states, such as pain, fear, or distress (9).

### The Five Freedoms and 3 Rs

The concept of the Five Freedoms originated in 1965, when the UK government commissioned an investigation, led by Professor Roger Brambell, into the welfare of intensively farmed animals ([http://www.afcd.gov.hk/english/quarantine/qua\\_vb/files/AW8.pdf](http://www.afcd.gov.hk/english/quarantine/qua_vb/files/AW8.pdf)). This investigation was partly in response to concerns raised by Ruth Harrison in her book, *Animal Machines* (10). Harrison described the poor conditions of many animals raised for food as agricultural systems were developed to produce higher profits with less regard for animal comfort and welfare (i.e., factory farming).

The subsequent Brambell Report (11) stated that animals should have the freedom to “stand up, lie down, turn around, groom themselves and stretch their limbs.” These recommendations

became known as Brambell's Five Freedoms. As a direct result of the Brambell Report, the Farm Animal Welfare Advisory Committee, and later the Farm Animal Welfare Council (FAWC), was established by the British Government. The FAWC refined the Five Freedoms concept, as described below (<http://www.fawc.org.uk/freedoms.htm>). Although the Five Freedoms have often been associated with farm animals, they also are significant and used when considering research animals in their various environments.

### **The Five Freedoms for Animal Welfare.**

1. **Freedom from Hunger and Thirst**—by ready access to fresh water and a diet to maintain full health and vigor.
2. **Freedom from Discomfort**—by providing an appropriate environment, including shelter and a comfortable resting area.
3. **Freedom from Pain, Injury, or Disease**—by prevention or rapid diagnosis and treatment.
4. **Freedom to Express Normal Behavior**—by providing sufficient space, proper facilities, and company of the animal's own kind.
5. **Freedom from Fear and Distress**—by ensuring conditions and treatment that avoid mental suffering.

Research outcomes using stressed or distressed animals have often been questioned for validity. Thus, maintaining consistent animal health and welfare is essential for reliable scientific discovery. Whenever possible, the responsible use of animals in research is guided by the 3 Rs: replacement, reduction, and refinement. Replacement involves evaluating the research to determine if the use of animals can be avoided altogether. Reduction refers to minimizing the number of animals necessary while making sure the research results will still be valid. Refinement refers to methods used to alleviate or minimize pain and distress, such as the use of anesthesia and medications to relieve pain. Incumbent upon every scientist using animals for research is a complete literature search that spans multiple disciplines, geographical boundaries, and languages to ensure the best use of animals and the best chance of an accurate outcome. Many institutions now have staff assigned to coordinate research studies throughout large academic centers, attempting to ensure that animals are used only when absolutely necessary.

### **The American College of Laboratory Animal Medicine**

The genesis of organized laboratory animal medicine resulted from the marked increase in biomedical research following World War II (<http://www.aclam.org/about-us/college-history>). The American College of Laboratory Medicine grew from efforts in the 1940s and 1950s, when veterinarians established the Animal Care Panel, which later became the American Association for Laboratory Animal Science. In 1961, the name was changed to the American College of Laboratory Animal Medicine (ACLAM), and those qualifying for full membership would be called Diplomates.

ACLAM Diplomates are veterinarians who specialize in laboratory animal medicine and are involved in a wide variety of activities: managing and directing animal resource facilities and programs; clinical medicine, surgery, and disease prevention; research and training; and assisting institutions in achieving compliance with animal care and use regulations. They must be familiar with the various requirements of agencies that fund animal research, ensure compliance for protecting the health and welfare of animals used for research, and sustain the integrity of an institution's entire research program.

## Animal Welfare Research Institute

In 2011, the American Humane Association launched the Animal Welfare Research Institute (AWRI). AWRI was tasked with providing scientific information for advancing animal health, welfare, and well-being. Such goals seemed timely as farmers asked for evidence on optimal housing systems for their animals, owners sought information on how their pet animals might participate in humane research studies, communities requested information on managing urban/wildlife conflicts, and the medical profession asked how the genomic era might leverage the many clues offered by the 60,000 vertebrate animals sharing our planet. American Humane Association's mission to advance wellness, welfare, and well-being for both animals and children seemed well-suited for AWRI, with accurate science being crucial for achieving the mission. Thus, AWRI identified multiple disorders that afflict both animals and children [e.g., cancer, diabetes, respiratory syncytial virus (RSV), asthma, food-borne illnesses, obesity, neurological disorders, and tuberculosis] and sought innovative collaborations whereby the genetic, nutritional, and environmental factors for health and disease might be identified. Leveraging the expertise of scientists working with companion animals, farm animals, and wildlife was deemed essential for optimizing the health and welfare of animals and children. Whereas some animal advocacy groups oppose all research involving animals, AWRI considers humanely conducted research, designed to benefit animals, to be extremely important. Such research might provide valuable information that advances both animal and human health. Research involving animals must be ethically and responsively conducted.

## LIMITATIONS OF THE CURRENT RESEARCH MODEL

### The War on Cancer Has Not Been Won

There are many things wrong with the way health research is financed and conducted in the United States. Because of this broken system, the war on cancer has not been won, blockbuster drugs are deemed unsafe after millions of people have taken them, women are told to take and then not to take hormone-replacement therapy as they age, and parents are uncertain of whether the foods and drinks consumed by their children are truly safe. An article published in *Newsweek* (12) suggested that the very framework of medical investigations may be wrong. At best, the existing system fails to optimize breakthrough discoveries. At worst, the system is dangerous. This leads to too few efficacious and safe therapies for children with cancer, confuses a public trying to prevent disease through proper eating, and ignores risk factors that cannot be assessed in the confinement of a research laboratory of inbred mice or beagles (13).

Margaret Cuomo is a physician and board-certified radiologist. She is also the sister of Governor Andrew Cuomo and CNN's Chris Cuomo. In her recent book, *A World Without Cancer: The Making of a New Cure and the Real Promise of Prevention* (14), Dr. Cuomo explains that our nation is over 40 years and \$90 billion dollars into the war on cancer, and still more than 1,500 people die from the disease every day. She suggests that our existing medical research system may be wrong—with experts and institutions at cross-purposes, and with little research time and federal funding spent on cancer prevention. In the United States, cancer is responsible for one out of every four deaths, and the incidence of some cancers is on the rise. Dr. Cuomo (14, p. xvii) asks, “Why have we settled for a medical system that allows cancer to be recast as a chronic and tolerable disease rather than one we should try to prevent?” In addition to the \$90 billion spent by the National Cancer Institute (NCI) since the war on cancer was declared by President Nixon, some 260 nonprofit organizations have also dedicated themselves to cancer, with budgets exceeding \$2.2 billion. Meanwhile, the rates of certain

cancers (kidney, liver, and thyroid cancer, melanoma, and lymphoma for adults; brain cancer and leukemia for children) are increasing according to NCI's Surveillance, Epidemiology, and End Results Program, which gathers statistics on cancer incidence, prevalence, and survival rates in the United States (<http://seer.cancer.gov/statistics/summaries.html>).

Cancer is but one example for describing the broken medical research system, but it is an important one when considering other species also afflicted with this disease. Although mice have been the mainstay for cancer research, it is now recognized that mice are inadequate for studying cancer. Homer Pearce, who once ran cancer research and clinical investigations at Eli Lilly, stated that mouse models are "woefully inadequate" for determining whether a drug will work in humans. "If you look at the millions and millions of mice that have been cured, and you compare that to the relative success, or lack thereof (in people), that we've achieved in the treatment of metastatic disease clinically," he says, "you realize that there just has to be something wrong with those models" (15). In fact, it might be the animals in our midst that will contribute mightily to scientific breakthroughs. Over 400 genetic diseases have been identified in dogs, and over 300 in cats. Many of these diseases are shared by people. The average life span of many companion animals is less than that for humans, allowing for strategic science to address naturally occurring diseases of the animals who share our homes.

Similar to the mortality rates for humans, one in four pet dogs over the age of two years will die of cancer. Interestingly, different breeds of dogs have different risks for specific cancers, which might hold clues for the genetic, dietary, and environmental risk factors for human cancers. Golden Retrievers in the United States are considered by many veterinary oncologists to have the highest risk for cancer (over 60%). However, even within the Golden Retriever breed, dogs born in the United States versus the United Kingdom seem to have different risks for specific cancers. For example, hemangiosarcoma is considered a common and often fatal cancer in US Golden Retrievers but is not cited as a common tumor in UK Golden Retrievers (16). Likewise, Greyhounds bred and born in the United States to race have a higher risk of developing osteosarcoma than Greyhounds registered through the American Kennel Club as purebreds, possibly owing to a genetic difference (<http://www.coutovetconsultants.com/blog/greyhound-osteosarcoma.html>). When possible, epidemiologists have attempted to quantify (incidence, prevalence) the occurrence of cancer in several breeds of dogs and evaluate genetic and nongenetic risk factors (17). Data sources in the United States are hard to quantify regarding the causes of canine deaths; it is important to note that the number of animals in popular breeds dying from cancer can be quite different from the percent of dogs dying of cancer when the total population of deceased dogs is considered.

Many dog breeds have developed over the past few hundred years and are also associated with risks for specific diseases. Thus, they offer a unique chance for studying genetic factors that may have led to such patterns of disease. As stated above, specific cancer types exist for several breeds of dogs (Table 1). Why? Owners of gray horses are told that their animals sooner or later are likely to develop melanoma. However, unlike melanomas in humans, the tumors in gray horses are often benign rather than malignant. Why? Naked mole rats might provide better clues on cancer prevention because they appear to be cancer resistant, having a life span exceeding 30 years (18). Why? The Tasmanian devil is now endangered owing to a contagious transmissible facial tumor cell. Transmissible venereal cell tumors in dogs are also transmitted by a tumor cell line without a known infectious etiology. What makes these cancers contagious? Why are pet cats at risk for vaccine-associated sarcomas to the level that veterinarians are instructed to vaccinate cats in specific limbs so that later amputation might be feasible? Virally induced cancers and chronic diseases that occur in domestic and wild cats (e.g., feline leukemia, feline infectious peritonitis, and feline immunodeficiency) do not occur in dogs. Why? Might not all of these examples

**Table 1 Breeds of US dogs at risk for specific cancers**

Breed	Type of cancer
Golden Retriever	Hemangiosarcoma, lymphoma
Labrador Retriever	Hemangiosarcoma, lymphoma
Standard Poodle	Squamous cell carcinoma of the digit
Greyhounds (non-American Kennel Club)	Osteosarcoma
Scottish Terrier	Transitional cell carcinoma, melanoma
Rottweiler	Osteosarcoma
Pug	Mast cell tumors
Flat-Coated Retriever	Histiocytic sarcoma
Boxer	Glioma, lymphoma
English Springer Spaniel	Mammary carcinoma

indicate that the animals in our world hold tremendous promise and clues to significant breakthrough—if only our research model allowed for it?

### Screening Tests and Personalized Medicine

Early detection of disease is often critical for proper and efficacious therapy. However, many existing screening tests have come under scrutiny. Until recently, many doctors and professional organizations encouraged yearly prostate-specific-antigen (PSA) screening for men beginning at age 50 (19). Some organizations recommend that men who are at higher risk of prostate cancer begin screening at age 40 or 45. However, as more has been learned about both the benefits and harms of prostate cancer screening, several organizations have begun to caution against routine population screening. Although some organizations continue to recommend PSA screening, there is widespread agreement that any man who is considering getting tested be first informed in detail about the potential harms and benefits.

Just as PSA screening is now confusing to both physicians and patients, so is the use of mammograms for detecting breast cancer in women. Potential harms of screening mammography include false-negative results, false-positive results, overdiagnosis, overtreatment, and radiation exposure (20). Marty Makary, a cancer surgeon at Johns Hopkins Hospital and associate professor of health policy at the Johns Hopkins Bloomberg School of Public Health, cautions that some screening efforts have gone too far (21). In addition to what might be invasive and unnecessary follow-up, emotional trauma from false alarms also takes its toll on women. What is becoming apparent is that screening tests cannot be the panacea for all members of a population and that personalized medicine may be required to tailor diagnostic tests and therapies for individual patients based on risk factors (e.g., familial history, ethnicity, race, age, and drug history).

Personalized medicine can use genomic and digital technologies to better determine appropriate tests and therapies for individual patients. Eric Topol, Chief Academic Officer at Scripps Health, studied the reasons for why a large population of people failed to respond to clopidogrel (22). A genetic variation in a significant minority of patients can prevent the drug from working or can limit its effectiveness, increasing a patient's risk for a potentially life-threatening heart attack. No longer can diagnostic tests or drugs be developed with only the population in mind. The needs

of individual patients must be addressed for both therapeutic efficacy and side effects. Future patients in clinical trials will be genetically screened, allowing researchers to better understand the differences between responders and non-responders to drug therapy. Although personalized medicine presents regulatory problems for drug approval, it is definitely the wave of the future as the field of pharmacogenomics continues to grow. It is also possible that drugs formerly removed from the market for adverse side effects might be reintroduced and suitable for subsets of the population.

### Research Efforts Are Fragmented, Clues Ignored, Incentives Misguided

Medical, veterinary, and wildlife scientists are incentivized to work largely in isolation. Thus, common disorders that affect both animals and people are often not studied with multidisciplinary partners to address novel strategies. Tuberculosis affects children, elephants, dairy cows, African buffalos, birds, and badgers—but few coordinated and multidisciplinary activities have emerged to consider how this disease might be eradicated, how vaccines might be developed, or how current multiple- and extreme-drug-resistant forms of the disease might be treated. Combinations of therapeutics used to treat drug-resistant tuberculosis in adults are sometimes associated with hepatotoxicity in children.

Respiratory syncytial virus (RSV) is a common illness in neonatal calves and children. Although a nasal vaccine is available to prevent the disease in dairy calves, there is no similar vaccine for children. Millions of children under the age of four acquire RSV each year, with many requiring hospitalization. The World Health Organization has targeted RSV for vaccine development for children. Perhaps the Global Vaccine and Immunization Research Forums—cohosted by the World Health Organization, the US National Institute of Allergy and Infectious Diseases, and the Bill & Melinda Gates Foundation—can include researchers from the veterinary and medical disciplines to discuss progress and challenges in vaccine development for RSV as part of the Global Vaccine Action Plan (<http://www.who.int/immunization/research/en/>).

Pet animals (dogs and cats) and children are frequently the victims of food-borne illnesses, such as those from *Escherichia coli*, *Salmonella*, *Campylobacter*, and *Listeria*. In addition, infant formula and pet foods contaminated with melamine have resulted in disease and/or death in pets and children (23, 24). An interdisciplinary, noncommercial study to evaluate the risks associated with various foods, food packaging, and products (pet toys, pacifiers, plastic bowls, and baby bottles) could benefit millions of animals and children. Noncommercial, nonpolitical research is also needed to better define healthy diets for pets and kids. For example, what are the ideal and affordable sources of protein for each?

Incentives for many academic researchers hardly promote risk-taking and breakthrough discovery. The ongoing academic publish-or-perish mentality for promotion and tenure values the number of refereed publications over the value of outcomes that might actually prevent disease and save lives. Facing ongoing state and federal funding cuts, academic institutions turn to recapturing lost dollars through tuition hikes, indirect cost recovery from grants, or partnerships with corporations more interested in selling drugs than preventing disease. The road for young scientists is especially challenging, as a change in federal funding has reportedly occurred over the past thirty years (25). According to Michael Levitt, a Nobel Prize winner in chemistry, people under the age of 40 get almost no money, and people over 65 get lots of money. Most Nobel Prize winners make their award-winning discoveries under the age of 40, suggesting that the reduction in funding for young scientists is not a good strategy for innovation.

Instead of having the luxury to innovate, scientists spend an inordinate amount of time seeking and managing grants. Alan Leshner, the CEO of the American Association for the Advancement



of Science, has also called for a rethinking of our science system (26). Dr. Leshner states that 42% of an American scientist's research time is spent on administrative tasks, much surrounding redundant reporting and assurance requirements that vary across agencies and universities. Scientists spend more time on writing and managing grants than on doing the research. As Dr. Stephen J. O'Brien, former Chief of the National Institutes of Health Laboratory for Genomic Diversity, stated, "One does not ask George Clooney or Meryl Streep to raise money for their movies or manage the stage setup. They are the talent for ensuring success for an outstanding performance as should be our scientists" (S.J. O'Brien, personal communication, March 18, 2014). We need a system that encourages our scientists to perform, not a system that puts roadblocks in their way and prevents productivity.

Dr. Leshner restated his concern about the United States maintaining scientific eminence, using agricultural research and development (R&D) as an example (27). US Department of Agriculture spending on R&D has declined by 26% (in constant dollars) over the past decade, whereas investments by China, India, and Brazil have increased dramatically. Agricultural challenges, such as dealing with new pests and pathogens, food-borne infections, environmental contamination, and antimicrobial resistance from subtherapeutic levels of drugs in animal feeds, are not likely to be adequately taken up by the private sector. These challenges are significant and growing (28); livestock production accounts for 75% of all agricultural lands and 30% of the Earth's land surface, making it the single largest anthropogenic land use (29). A recent analysis suggests that ammonia (present in fertilizers and animal waste) does more damage to human health than previously thought. Ammonia reacts with other air pollutants to create tiny particles that can lodge deep in the lungs, causing asthma attacks, bronchitis, and heart attacks (30). Given the current trends for developing countries to consume more animal protein, an area larger than the United States is estimated to be converted to agriculture by 2050 (31). Adequate funding is needed for US research endeavors, but also needed are strategic priorities, collaborative efforts, and the will of a nation to retain scientific eminence and keep its citizens healthy. This speaks to the very heart of a nation's spirit and commitment to a better future.

### **Lack of Pediatric Research**

Our children deserve the very best medical system, with research conducted to benefit their unique metabolism and systems. According to the National Heart, Lung and Blood Institute, children have often had to accept medicines and treatments based on what is known to work in adults. As a society, we should not agree to these hand-me-down approaches (<http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php>). As stated by Dr. Renee Jenkins, pediatrician and President of the American Academy of Pediatrics (2007–2008), "Children are not little adults. They are unique" (32, p. 10).

The incidence and/or prevalence of several childhood diseases are increasing in the United States, begging for urgency in strategic research to prevent and treat our kids. Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, some forms of cancer, obesity, type 2 diabetes, and food and skin allergies have all been reported to increase during the past decade. The Centers for Disease Control and Prevention (CDC) state that ADHD is a serious public health problem that is believed to have a noticeable impact on social, economic, educational, and health care delivery systems (33). Unfortunately, research to provide demographic and descriptive statistics for children and adults with ADHD is not available. Thus, there are disparities in identification, access to treatment, and reports of the manifestation of ADHD and its comorbidities. Environmental and genetic risk factors have not been adequately researched. Lack of

information exists, even as the CDC reports that there may be two million more children afflicted with ADHD in 2011 than in 2003 (34).

Even when research is conducted on childhood illnesses, like asthma, the results do not always translate to the pediatricians and parents. According to the CDC, over 10 million US children under the age of 18 (14%) have been diagnosed with asthma (35). Allergies in household members are often cited as a reason for relinquishing a pet cat to an animal shelter (36), and researchers have demonstrated potent allergens in feline saliva, leading some companies to attempt to breed and sell allergy-free cats (37). Although many physicians have associated cats with atopic dermatitis and asthma in children, this may be incorrect depending on the age of the child. In one study, cat exposure had a strong and independent effect in reducing the risk of developing asthma across all analyses (38). Such effects may be age dependent, with protection against the development of asthma symptoms when children under the age of five are exposed to cats (39). Thus, parents of very young children might not want to get rid of their cat just because they are concerned their young child might develop asthma (40). Exposure to cat allergens, however, is associated with allergies and asthma in others. Therefore, just as adults need personalized medicine and research, so do children.

### Lack of Personalized Research

**Animals (species, breed, age, neuter status).** For many years, cats were treated as small dogs. Nothing could be further from the truth. Cats are strictly carnivores in the wild, whereas dogs are omnivores and can sustain life from both plant and animal energy sources. Cats that eat solely commercial dog foods, without supplemental taurine, can develop visual impairment (41). Some medications that are safe for dogs and humans can be toxic for cats (42). For example, cats are relatively deficient in enzyme glucuronyl transferase activity, which conjugates acetaminophen to the nontoxic metabolite (glucuronic acid) for excretion (43). Thus, administration of acetaminophen can result in the death of a cat when given by an uninformed owner.

Even within dogdom, veterinarians understand that one dog breed does not equate to another. No species on the planet has more size diversity than the canine species, with dogs ranging in weight from under 5 lb to over 200 lb. Dog breeds are also diverse with respect to risk for disease and adverse side effects from certain therapies. For example, ivermectin is a common drug used to treat heartworm disease and other parasitic diseases in dogs. Although the drug is used safely in many breeds, dogs of some breeds (e.g., Collie, Old English Sheepdog, and Shetland Sheepdog) can be especially sensitive to this medication. This sensitivity has been shown to result from a mutation in the multidrug resistance (MDR1) gene. One in three Collies in the United States may be homozygous for the mutation, leading to a potentially acute and fatal neurotoxicosis (44). Dogs can now be tested for the MDR1 mutation at Washington State University's College of Veterinary Medicine, allowing for personalized, efficacious, and safe therapy (45). Genetic tests are also being developed for both cats and dogs to identify unique genetic characteristics and define a more personalized approach for diets, diagnostic tests, disease risk factors, and therapies (<http://www.wisdompanel.com>; 46).

The neuter status of cats and dogs is also associated with health and disease. Pets neutered prior to puberty have a significantly reduced risk of developing mammary carcinoma. Some recent research (47), however, has cautioned that pets of some breeds (but not all) neutered early in life might be more at risk for other types of cancers and orthopedic disorders. These are examples for why personalized medicine must also be considered in veterinary medicine when attempting to provide the optimal chance for improving health in our animals.

**Humans (gender, race, ethnicity, age).** The effect of diets and drugs on people of different genders, races, ethnicities, and ages can be quite variable, but diets and drugs are often provided or developed with consideration for populations rather than for individuals. In the United States, approximately 75% of African-Americans have the potential for symptoms of lactose intolerance (48). Race and ethnicity can also account for differences in pharmacokinetics, pharmacodynamics, and response to therapy (49). Potential causes of variability in drug response include extrinsic factors like food and use of other drugs. Intrinsic factors include gender, race, ethnicity, age, weight, renal and hepatic function, and genetic differences in the expression of enzymes that metabolize or transport drugs, or in the expression of drug therapy. For example, race has been reported to contribute to variability in dosing requirements for warfarin as an anticoagulant, with African-Americans often requiring higher doses and Asians requiring lower doses than Caucasians (49). Even within a population, subsets, groups, or individuals can respond very differently to various drugs, suggesting that new paradigms are needed when evaluating drugs that perhaps should be personalized to each patient. Such personalization challenges existing regulatory agencies, such as the Food and Drug Administration, in overseeing the development and approval of therapies that are tailored for individual patients.

Clinical trials for new drugs can skew data results on the basis of selected enrollees, with adverse side effects sometimes noted after a drug is on the market. The fact that pharmaceutical companies sponsor and run many investigative trials calls into question the potential for bias when selecting patients who might be thought to have a higher chance for efficacy and a lower chance for side effects. Roughly 53% of new cancer diagnoses, for example, are in people over the age of 65, but this age group accounts for just 33% of participants in cancer drug trials (50). Although younger enrollees with cancer might need to be included in clinical trials, should their data be extrapolated to older enrollees with different metabolisms, organ functions, and lifestyles? Some companies are now developing diagnostic tests alongside therapies. Sixty percent of the new drugs being developed by Genentech/Roche are being developed with a companion diagnostic test to identify patients who are most likely to benefit.

## **A NEW MEDICAL RESEARCH MODEL: CHANGING THE PARADIGM FOR ADVANCING HEALTH**

A new medical research model for advancing human and animal health is drastically needed. The new model would involve global partners, spanning various disciplines, to collaborate on disease prevention and to develop innovative, efficacious, and gentler therapies for treating acute and chronic disease. Priorities would be established, scientists and funding agencies would convene, and strategies would be developed. Biases and conflicts would be addressed and minimized, with a model developed that is both transparent and participatory for the public. A model with goals to prevent disease, promote health, and optimize welfare and well-being should be an ethical obligation for governments, academic institutions, and nonprofit agencies whose missions are to protect their citizens. It should also be a goal for any business selling drugs, diets, and other products to benefit human and animal health. Research teams should span geographical areas, languages, and systems (e.g., mathematics, physics, engineering, and computational analytics) and should include only those members who are truly collaborative, dedicated, and visionary.

### **The Scientists**

Scientists on the teams would include those with traditional scientific training, with many experienced researchers mentoring new talent. The priorities for research funding would be

for young, innovative thinkers unencumbered by old paradigms—many of whom today are leaving research owing to lack of support. In addition, scientific teams would include citizen scientists, those individuals in our society who could help collect data and/or biological samples, or who could bring immediate relevance to a discipline through their direct association with the disease being studied. Teams would include medical, veterinary, animal science, and wildlife scientists—taking advantage of the clues from thousands of species on the planet. Language barriers would be minimized by new technologies, with global teams convening in person or via the Internet. Incentives would be structured so that every team member would be rewarded for collaboration versus competition. Teams would include members from ancillary fields—such as mathematics, physics, engineering, and computational analytics—and would also include input from ethicists, business entrepreneurs, marketing professionals, psychologists, economists, environmentalists, public health scientists, and strategists. Research addressing disease prevention would receive at least 50% of the funding. Addressing diseases and disorders affecting the world’s children would also receive a high priority for funding.

### The Oversight Agency

A new medical research model will require a new type of oversight. Existing oversight agencies often have inherent biases that prevent truly innovative science from occurring.

**Federal oversight.** Congress provides oversight for federal agencies, such as the National Institutes of Health, US Department of Agriculture, US Fish and Wildlife Service, CDC, Food and Drug Administration, National Science Foundation, and many others, allowing elected representatives and senators to monitor the use of taxpayer dollars for keeping us safe and promoting our nation’s health. Although such oversight is understandable, Congress wishing to set funding priorities or determine how research grants are reviewed and evaluated is less understandable and somewhat troubling. In 2013, Rep. Lamar Smith (Chairman of the House Science, Space and Technology Committee) and Rep. Eric Cantor (Majority leader of the US House of Representatives) wrote an opinion piece for *USA Today* questioning the review process for the National Science Foundation (51, p. 28):

Asking questions about these and other grants in order to obtain more information about why they were selected and how they benefit the American people is good policy and good government. If NSF has nothing to hide, why not provide Congress and the American public with a meaningful justification for why these grants were chosen over thousands of others?

Reprioritizing the government’s research spending in favor of improving Americans’ quality of life is not anti-science. It is common sense. We look forward to working with the NSF to address these concerns and to create a better process for evaluating research proposals.

Certainly, Congress has an obligation to provide oversight for all federal agencies receiving funding. Just as the new medical research model calls for prioritizing and strategizing to address health and disease, so might Congress. What is troubling, however, is that few Americans believe that Congressional members are capable of working effectively together to address society’s needs. Americans’ approval of the way Congress is handling its job dropped to 9% in 2013, the lowest in Gallup’s 39-year history of asking the question (52). The public questions whether Congress could reliably and collaboratively prioritize research to make Americans healthier, without inherent political or social bias.

**Academic oversight.** A new paradigm at academic centers will need to emerge for rewarding scientists before existing centers can provide oversight for a truly collaborative medical research model. This does not mean that collaborative research is not occurring today at college and universities; rather, it means that funding for innovative science, incentives for scientists, and potential opportunities are limited when thinking of health challenges that exist within the current academic model. Currently, incentives are weighted on outputs rather than outcomes that benefit society. Such outputs include the number of scientific publications in refereed and prestigious journals, indirect overhead revenue secured through grants, or patents and future revenue from product development. Sharing of information is often limited when an academic center fears the loss of revenue by premature disclosure of data.

The Bayh-Dole Act of 1980 (35 U.S.C., §200–212) allowed universities to control their intellectual property, such as patents, generated from federally funded research. With a patent in hand, universities could exclusively license the patent to businesses and benefit from the licensing revenue. Although such public-private partnerships can certainly benefit society, there is also concern about the lack of expediency in getting new information (and therapy) to the public quickly versus ensuring that maximum R&D profits might be realized by a business partner. Researchers will often withhold presenting information at conferences before patents are issued, or because information included in proceedings will not be accepted in those types of publications required for tenure and promotion.

**Nonprofit associations, agencies, and foundations.** Venture philanthropists, social entrepreneurs, market-based philanthropy, charities, and patient advocacy groups all have an interest in advancing a new medical research model. What seems certain is that no single entity can advance human and animal health in isolation. A recent special philanthropy issue by *Forbes* (53) suggests that cooperation will be critical for addressing some of the world's major issues, with success being defined as both immediate alleviation of physical suffering and needs and long-term impact. The world's wealthiest people plan to give away a greater proportion of their wealth than ever before. Nearly one in five people plan to give away more than half of their wealth upon their death. Thus, there is no better opportunity than now to use such contributions wisely to prevent, diagnose, and treat disease. Donors will want to know that their dollars are spent wisely, with the best chance for improving health outcomes.

The cost to have one's entire genome sequenced has fallen to near \$1,000, making this an affordable diagnostic test (54, 55). Contrast this to the first human genome sequenced, which required \$3 billion in public funds and 13 years to complete. Now children and animals with rare diseases could be diagnosed. People with cancers that are nonresponsive to therapies are today receiving personalized therapy based on the genetic profile of their tumor.

Following the sequencing of the first human genome, progress in genetic-based medicine seemed slow for many years. The notion that sequencing a genome could lead to cures for cancer, diabetes, and brain disease has not been realized as quickly as promised. However, scientists and entrepreneurs are once again excited about genetic-based medicine. At the center of the excitement are new technologies that reduce cost and time for genetic sequencing. A San Diego-based company (Illumina) that develops, manufactures, and markets integrated systems for the analysis of genetic variation and biological function recently announced that it reduced the cost of genome sequencing by a factor of 10 when it unveiled sequencers—approximately the size of a photocopier—that are basically DNA supercomputers (54). The new sequencers can complete 20,000 human genomes in a year. Such rapidity in results now allows scientists to compare and contrast human and animal genomes, unveiling the mask of commonality that leads to health and disease.

Although nonprofit organizations may not all be science based, many have mission statements for advancing health, welfare, and/or well-being on the basis of science and sound evidence. Patient advocates are interested in rapid and transparent data sharing so that loved ones have the best chance for survival. Although the public understands the need for businesses to make a profit, they do not understand why patents and profits should stand in the way of rapid progress for the people and pets they love. Thus, philanthropists are beginning to create their own nonprofits or are massively funding existing ones. What is needed is a strategy to ensure scientific rigor and expediency, goals for both preventing and treating disease, and methods and metrics to ensure a healthier world for all.

Many nonprofits are now working to bring diverse scientists together. The 2009 and 2013 Skippy Frank Translational Comparative Medicine Conferences (<http://immunol.stanford.edu/conferences/register.html>) were supported by a philanthropist/researcher who is actively seeking new medical research models. In 2013, the American Humane Association held a conference at the PricewaterhouseCoopers headquarters in New York to bring medical and veterinary researchers together to consider how personalized medicine for animals and people might be accelerated. In the same year, a Be Humane Summit was held in Florida that also addressed the need for a new research model to advance wellness, welfare, and well-being for children and animals. In 2014, medical and veterinary scientists convened in Kentucky to consider clues from the animal kingdom that might shed light on pulmonary fibrosis, a disease that is often fatal in humans and also affects West Highland Terriers, cats, horses, and donkeys. This conference was organized by both the Westie Foundation of America and the Coalition for Pulmonary Fibrosis and addressed preventing, diagnosing, and treating pulmonary fibrotic diseases across species (<http://www.pulmonaryfibrosis.org/eventscalendar2014>). These are but a few examples of efforts whereby nonprofit organizations are attempting to raise revenue for research, but in a manner that requires scientists, working with numerous species, to address health and disease collectively.

**The public.** Citizens understand the need for a new medical research model better than anyone. They want gentler therapies for treating cancer; they want to know how to feed their children and animals to prevent chronic illness; and they want scientists to collaborate between disciplines, countries, and species to create new knowledge. When possible, they want to be engaged and help with research as citizen scientists. They are willing to participate in clinical research trials (either themselves or their animals) but want assurance that studies are well designed and humane. They will be far less likely to support research that uses animal models that do not work, or research that is primarily positioned to make profit over true innovation.

The public also wants direct access to diagnostic tests and results for themselves and for their family members (humans and pets). This is likely a reason that customer-based genetic tests, like 23AndMe (<http://www.23andme.com/>), became popular. Although 23AndMe stopped selling the genetic-based tests in 2013 owing to regulatory issues with the Food and Drug Administration (56), cofounder Anne Wojcicki believes genetic tests will be critical in the future for preventive medicine and for reducing the cost of health care. Parents and pet owners want firsthand information on laboratory tests that can affect the future health of children and animals. Recent regulations seem to support this desire. In 2014, the Obama administration released new regulations that allow patients to get test results without going through their doctor first (57). The rules are part of an effort to empower patients and give them more control over their health care. Physicians and veterinarians must work collaboratively with patients and owners to provide assistance with interpretation of genetic results. These health care professionals will also need to be well trained in genetics, environmental toxicology, and

nutrition—integrating multiple disciplines for advancing health. It is no longer acceptable to withhold information from people owing to a patriarchal belief that the public needs protection from results that could be misinterpreted or troubling. Not so many decades ago, diagnoses of cancer and other serious diseases were also withheld from patients. It is time for a true partnership to evolve with the new model. No one has a more vested interest in medical research than those affected by disease, or those wishing to prevent disease for those they love. The public will be an eager learner—whether the medical profession provides the information or someone else does.

**The animals.** Tremendous potential for discovery exists if scientists collaborate to study the animals in our midst. Millions of years have led to evolutionary systems of protection for survival. Mutations have also resulted in species, breeds, and individuals. As our environment changes, animals serve as potent sentinels for environmental risk factors. As animals and humans participate in the same studies, institutional animal care and use committees and institutional review boards will also collaborate in the future.

Studies can be designed whereby the public engages in the process, animals are humanely treated, and outcomes are critically assessed with good metrics. Some studies will convene scientists to address significant health issues affecting both animals and people (e.g., cancer, tuberculosis, arthritis, and diabetes). Other studies will assess the benefit of animals in improving the lives of humans. Two such examples include the Morris Animal Foundation's Canine Lifetime Health Project (<http://www.caninelifetimehealth.org/>) and the American Humane Association's Canines and Childhood Cancer Study (58).

- **Morris Animal Foundation Canine Lifetime Health Project**—Owners and veterinarians will be following approximately 3,000 Golden Retrievers throughout their lifetimes to determine risk factors for disease. The study was partially designed and based on the Framingham Heart Study, which began in 1948 to assess risk factors for heart disease in men (<http://www.framinghamheartstudy.org/>). Detailed information will be collected on diets, drugs, and environmental exposures that the dogs encounter. Biological samples will be collected to identify genetic risk factors and diagnostic prognosticators for early detection of disease. Information gleaned from the animals just might aid in potential discoveries relevant for their human family members.
- **American Humane Association Canines and Childhood Cancer Study**—Zoetis and the Pfizer Foundation have partnered with the American Humane Association to investigate the impacts of animal-assisted therapy on pediatric oncology patients and their families. The goals of this collaboration are to promote innovation, evidence-based research, practice improvements, and knowledge advancement to further the field of research on human-animal interactions and the treatment of cancer in children.

As Barbara Natterson-Horowitz, cardiology professor at the David Geffen School of Medicine at University of California, Los Angeles, states in her book, *Zoobiquity* (59), animal and human commonality can be used to diagnose, treat, and heal patients of all species. We need to listen to one another, learn from one another, and know that we are all creatures on a planet that holds the secrets to our future health. It is incumbent upon us all to develop the model that can minimize conflict and optimize discovery. Lessons can be learned from the animals in our midst—in homes, farms, and forests. As wildlife scientists are brought into the model, perhaps knowledge of frogs being born with abnormal genitalia might be a clue for pediatricians wondering why so many little girls are now entering puberty at age 7 (60), and why hypospadias (a misplacement of the urethra) is twice as common in little boys as it once was (61).

## SUMMARY

A new medical research model must emerge and has already begun to do so. This model will use the expertise of scientists working with diverse species, giving clues on what leads to health and disease. The strategies will be challenging, but the potential opportunities are immense. It is our society's obligation to ethically and responsibly advance the health of the Earth's animals and people, knowing that as we help the creatures, we are also helping ourselves.

## DISCLOSURE STATEMENT

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## LITERATURE CITED

1. Kaufman W. 1968. 1596–1650 Rene Descartes. In *Philosophic Classics: Bacon to Kant*, ed. W Kaufmann, pp. 21–80. Englewood Cliffs, NJ: Prentice-Hall
2. Wilson SD. 2010. Animals and ethics. In *Internet Encyclopedia of Philosophy: A Peer-Reviewed Academic Resource*. <http://www.iep.utm.edu/anim-eth/>
3. Kean H. 1995. The 'smooth cool men of science': the feminist and social response to vivisection. *Hist. Workshop J.* 40(1):16–38
4. Ed. Encycl. Br. 2013. Sir William Maddock Bayliss. In *Encyclopedia Britannica Online*, updated Aug. 23. <http://www.britannica.com/EBchecked/topic/56894/Sir-William-Maddock-Bayliss>
5. Natl. Anti-Vivisect. Soc. Who wants a Royal Commission on vivisection? [http://www.navs.org.uk/about\\_vivisection/27/43/348/](http://www.navs.org.uk/about_vivisection/27/43/348/)
6. Smith D. 2002. In brief: rats, mice and birds excluded from Animal Welfare Act. *Monit. Psychol.* 33(7):14
7. Rollin BE. 2012. Ethics of medical research with animals: the moral status of invasive animal research. *Hastings Cent. Rep.* 42(6):1–6. <http://animalresearch.thehastingscenter.org/report/the-moral-status-of-invasive-animal-research/>
8. Int. Assoc. Study Pain. 2014. *IASP Guidelines for the Use of Animals in Research*. Washington, DC: Int. Assoc. Study Pain. <http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1217>
9. World Organ. Anim. Health. 2014. Animal welfare. In *Terrestrial Animal Health Code*, Article 7.1.1. Paris: World Organ. Anim. Health. <http://www.oie.int/en/international-standard-setting/terrestrial-code/access-online/>
10. Harrison R. 1964. *Animal Machines*. London: Vincent Stuart Publ.
11. Brambell FWR. 1965. *Report of the Technical Committee to Enquire into the Welfare of Animals Kept Under Intensive Livestock Husbandry Systems*. London: Her Majesty's Station. Off. <http://www.defra.gov.uk/fawc/about/five-freedoms/>
12. Begley S. 2011. Why almost everything you hear about medicine is wrong. *Newsweek*, Jan. 15
13. Ganzert RR, Olson PN. 2012. *A new paradigm for medical research, evidence-based policy and humane solutions*. Spec. Rep., Am. Hum. Assoc. Res. Policy Inst., Am. Hum. Assoc., Washington, DC
14. Cuomo MI. 2012. *A World Without Cancer: The Making of a New Cure and the Real Promise of Prevention*. New York: Rodale Inc.
15. Leaf C. 2004. Why we're losing the war on cancer. *Fortune*, March 22, pp. 76–82, 84–86, 88
16. Dobson JM. 2013. Breed-predisposition to cancer in pedigree dogs. *ISRN Vet. Sci.* 2013:941275
17. Butler LM, Bonnett BN, Page RD. 2012. Epidemiology and the evidence-based medicine approach. In *Small Animal Clinical Oncology*, ed. SJ Withrow, DM Vail, RD Page, pp. 68–82. St. Louis, MO: Elsevier/Saunders
18. Univ. Haifa. 2013. *The naked mole rat's secret to staying cancer free*. Press Release, July 17
19. Natl. Cancer Inst. 2012. *Fact Sheet: Prostate-Specific Antigen Test (PSA)*. Bethesda, MD: Natl. Cancer Inst. Natl. Inst. Health. Reviewed July 24, 2012. <http://www.cancer.gov/cancertopics/factsheet/detection/PSA>



20. Natl. Cancer Inst. 2012. *Fact Sheet: Mammograms*. Bethesda, MD: Natl. Cancer Inst. Natl. Inst. Health. Reviewed July 24, 2012. <http://www.cancer.gov/cancertopics/factsheet/detection/mammograms>
21. Makary M. 2014. The cost of chasing cancer. *Time*, Feb. 27
22. Winslow R. 2012. When Plavix may not work. *The Wall Street Journal*, updated March 22. <http://online.wsj.com/news/articles/SB10001424052748704841304575138091114112552>
23. Times Top. 2014. Melamine—China tainted baby formula scandal. *The New York Times*, March 17. <http://topics.nytimes.com/top/reference/timestopics/subjects/m/melamine/index.html>
24. Levy S. 2007. Melamine death toll passes 8,000 pets. *Newser*, May 4. <http://www.newser.com/story/1927/melamine-death-toll-passes-8000-pets.html>
25. AAAS News. 2013. U.S. Nobel Prize winners honored in D.C. *AAAS News*, Nov. 25. <http://membercentral.aaas.org/announcements/us-nobel-prize-winners-honored-dc>
26. Leshner AI. 2011. Rethinking the science system. *Science* 334:738
27. Leshner A. 2013. Maintaining science eminence. *Science* 341:820
28. Machovina B, Feeley KJ. 2014. Taking a bite out of biodiversity. *Science* 343:838
29. Livest. Environ. Dev. 2006. *Livestock's Long Shadow: Environmental Issues and Options*. Rome: Food Agric. Organ. <http://www.fao.org/docrep/010/a0701e/a0701e00.htm>
30. Stokstad E. 2014. Ammonia pollution from farming may exact hefty health costs. *Science* 343:238
31. Tilman D, Fargione J, Wolff B, D'Antonio C, Dobson A, et al. 2001. Forecasting agriculturally driven global environmental change. *Science* 292:281–84
32. Cure Child. Cancer. 2010. Understanding the scope and challenges of childhood cancer. White Pap., Cure Child. Cancer, Atlanta, GA. <http://www.curechildhoodcancer.org/wp-content/uploads/2010/06/CURE-State-of-Childhood-Cancer-White-Paper-04-09.pdf>
33. Cent. Dis. Control Prev. 2013. *Attention-Deficit/Hyperactivity Disorder (ADHD)*. Atlanta, GA: Cent. Dis. Control Prev. Updated Nov. 21. <http://www.cdc.gov/ncbddd/adhd/research.html>
34. Cent. Dis. Control Prev. 2013. *Key Findings: Trends in the Parent-Report of Health Care Provider-Diagnosis and Medication Treatment for ADHD: United States, 2003–2011*. Atlanta, GA: Cent. Dis. Control Prev. Updated Dec. 3. <http://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html>
35. Bloom B, Cohen RA, Freeman G. 2011. Summary health statistics for U.S. children: National Health Interview Survey, 2011. *Vital Health Stat.* 10:254. [http://www.cdc.gov/nchs/data/series/sr\\_10/sr10\\_254.pdf](http://www.cdc.gov/nchs/data/series/sr_10/sr10_254.pdf)
36. Natl. Counc. Pet Popul. Study Policy. 1999. *Exploring the Surplus Cat and Dog Problem*. New London, MN: Natl. Counc. Pet Popul. Study Policy. <http://petpopulation.org/exploring.pdf>
37. Pepling R. 2006. “Hypoallergenic” cats for sale, U.S. firm announces. *National Geographic News*, June 9. <http://news.nationalgeographic.com/news/2006/06/060609-allergies-cats.html>
38. Gaffin JM, Spergel JM, Boguniewicz M, Eichenfield LF, Paller AS, et al. 2012. Effect of cat and daycare exposure on the risk of asthma in children with atopic dermatitis. *Allergy Asthma Proc.* 33(3):282–88
39. Columbia Univ. Mailman Sch. Public Health. 2008. Early life exposure to cats may reduce risk of childhood allergies and asthma symptoms. *ScienceDaily*, May 22. <http://www.sciencedaily.com/releases/2008/05/080520150717.htm>
40. Am. Acad. Allergy Asthma Immunol. 2014. *Pet Allergy Overview*. Milwaukee, WI: Am. Acad. Allergy Asthma Immunol. Accessed March 18. <http://www.aaaai.org/conditions-and-treatments/allergies/pet-allergy.aspx>
41. Yuill C. 2014. *Taurine in Cats*. Los Angeles, CA: VCA Anim. Hosp. Accessed March 18. <http://www.vcahospitals.com/main/pet-health-information/article/animal-health/taurine-in-cats/3857>
42. Banfield Pet Hosp. 2014. *Differences Between Cats and Dogs*. Portland, OR: Banfield Pet Hosp. Accessed March 18. <http://www.banfield.com/pet-health-resources/preventive-care/behavior/differences-between-cats-and-dogs>
43. Mladenovic D. 1998. Tylenol (acetaminophen) toxicosis in cats. *ADDL Diagn. Forum Newsl.* Spring 1998. <http://www.addl.purdue.edu/newsletters/1998/spring/acet.shtml>
44. Neff MW, Robertson KR, Wong AK, Safra N, Broman KW, et al. 2004. Breed distribution and history of canine *mdr1-1Δ*, a pharmacogenetic mutation that marks the emergences of breeds from the collie lineage. *Proc. Natl. Acad. Sci. USA* 101(32):11725–30

45. Coll. Vet. Med. 2014. *Multidrug Sensitivity in Dogs*. Pullman, WA: Wash. State Univ. Updated March 12. <http://www.vetmed.wsu.edu/depts-VCPL/>
46. Coll. Vet. Med. 2013. *The Lyons' Den Is Moving into the Tiger's Lair*. Columbia: Coll. Vet. Med., Univ. Missouri. <http://vetmed.missouri.edu/news/Lyons2013.html>
47. de la Riva GT, Hart BL, Farver TB, Oberhauer AM, Messam LL, et al. 2013. Neutering dogs: effects on joint disorders and cancers in Golden Retriever. *PLOS ONE* 8(2):e55937
48. Byers KG, Savaiano DA. 2005. The myth of increased lactose intolerance in African-Americans. *J. Am. Coll. Nutr.* 24(6):569S–73S
49. Yasuda SU, Zhang L, Huang S-M. 2008. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. *Clin. Pharmacol. Ther.* 84(3):417–23
50. Leaf C. 2013. Opinion pages: Do clinical trials work? *The New York Times*, July 13. [http://www.nytimes.com/2013/07/14/opinion/sunday/do-clinical-trials-work.html?pagewanted=all&\\_r=0](http://www.nytimes.com/2013/07/14/opinion/sunday/do-clinical-trials-work.html?pagewanted=all&_r=0)
51. Cantor E, Smith L. 2013. Rethinking science funding: Bronze Age Cyprus and Chinese auto shows might not be the kind of high priority research topics that need federal cash. *USA Today*, Sept. 30
52. Newport F. 2013. Congressional approval sinks to record low. *Gallup Polit.*, Nov. 12. <http://www.gallup.com/poll/165809/congressional-approval-sinks-record-low.aspx>
53. Brown P. 2013. Entrepreneurs can save the world. Special Issue, *Forbes*, Dec. 2
54. Vance A. 2014. Would you pay \$1,000 to find out how you might die? *Bloomberg Businessweek*, Jan. 20–26, pp. 54–57
55. Hayden EC. 2014. The \$1,000 genome. *Nature* 507(7492):294–95
56. Wojcicki A. 2013. 23AndMe provides an update regarding FDA's review. *23andMe* (blog), Dec. 5. <http://blog.23andme.com/news/23andme-provides-an-update-regarding-fdas-review/>
57. Kaiser Health News. 2014. *New Rule Allows Patients Direct Access to Lab Results*. Menlo Park, CA: Kaiser Health News. <http://www.kaiserhealthnews.org/Daily-Reports/2014/February/04/new-patient-access-rules.aspx>
58. Am. Hum. Assoc. 2014. *Canines and Childhood Cancer (CCC): Examining the Effects of Therapy Dogs with Childhood Cancer Patients and Their Families*. Washington, DC: Am. Hum. Assoc. <http://www.americanhumane.org/interaction/programs/animal-assisted-therapy/canines-and-childhood-cancer.html>
59. Natterson-Horowitz B. 2012. *Zoobiquity: What Animals Can Teach Us About Health and the Science of Healing*. New York: Random House
60. Szabo L. 2011. Girls hit puberty earlier than ever, and doctors aren't sure why. *USA Today*, April 10. Updated April 14. <http://usatoday30.usatoday.com/news/health/wellness/story/2011/04/Girls-hit-puberty-earlier-than-ever-and-doctors-arent-sure-why/45989054/1>
61. Kristof N. 2012. How chemicals affect us. *The New York Times*, May 2. [http://www.nytimes.com/2012/05/03/opinion/kristof-how-chemicals-change-us.html?\\_r=0](http://www.nytimes.com/2012/05/03/opinion/kristof-how-chemicals-change-us.html?_r=0)



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