ONE HEALTH

Companion animals: Translational scientist’s new best friends

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Knowledge and resources derived from veterinary medicine represent an underused resource that could serve as a bridge between data obtained from diseases models in laboratory animals and human clinical trials. Naturally occurring disease in companion animals that display the defining attributes of similar, if not identical, diseases in humans hold promise for providing predictive proof of concept in the evaluation of new therapeutics and devices. Here we outline comparative aspects of naturally occurring diseases in companion animals and discuss their current uses in translational medicine, benefits, and shortcomings. Last, we envision how these natural models of disease might ultimately decrease the failure rate in human clinical trials and accelerate the delivery of effective treatments to the human market.

It is undeniable that genetic manipulation of laboratory animals, technological advances such as genome editing, and the capacity to induce disease in a predictable fashion have all provided crucial platforms for the study of basic mechanisms of disease. At the same time, preclinical studies in mice have often proven to be poor predictors of outcomes of human clinical trials (1, 2). The questionable relevance of preclinical rodent disease models to clinical efficacy studies likely contributes to the high failure rates of human clinical trials. It is this progression from safety-focused to efficacy-focused clinical trials that has resulted in serious questions about the utility of mouse models as platforms for translational research (2, 3). Highly inbred and genetically modified laboratory animals kept in homogeneous and closely regulated environments are markedly different from humans who exhibit genetic variability, have diverse diets and personal habits, and live in varied environments.

Cross-disciplinary collaborations among basic, translational, engineering, and clinical scientists have initiated translational studies in an effort to harness naturally occurring diseases in companion animals to accelerate drug and device development. These synergistic collaborations are identifying clinically relevant models that offer the opportunity to conduct rigorous translational investigations. Naturally occurring diseases in companion animals might better reflect the complex genetic, environmental, and physiological variation present in humans, and enrollment and participation of companion animals in clinical trials mirror that of the human health care systems. Animal owners seek high levels of veterinary care and often sustain long-term treatment regimens for chronic disorders. Thus, companion animals may provide clinically relevant models of human diseases and serve as a crucial link between basic and preclinical research in small-animal–induced disease models and human clinical trials—a bidirectional, synergistic pathway in which both veterinary patients and human patients benefit from the implementation of this new translational research paradigm.

HARNESSING VETERINARY MEDICINE

Before a drug or medical device is approved by the U.S. Food and Drug Administration (FDA) for marketing in the United States, it must undergo rigorous scientific testing to ensure tolerable levels of toxicity and a demonstrable beneficial biological response (4). New drug development starts with in vitro toxicity studies in human and animal tissue cultures followed by in vivo animal studies that are designed to determine the metabolic, pharmacokinetic, and pharmacodynamic characteristics of the drug as well as its toxicity profile (Fig. 1). Typically, these animal studies are conducted in more than one animal species (a rodent and a nonrodent species). Although incorporation of data from proof-of-concept in vivo studies in Investigational New Drug application submission is encouraged by FDA (5), proof-of-concept efficacy studies are not mandated prior to the initiation of human phase 1 (safety) clinical trials (4). A recent paper by Hay et al. (3) calculated that, during a 9-year period (2003–2011), the likelihood that a new therapeutic compound entering phase 1 clinical trials would achieve FDA approval was 10.4% (n = 5820 candidate new drugs). The authors further determined that the phase 2 to phase 3 transition (that is, the transition from safety-focused to efficacy-focused studies) displayed the lowest success rate at 32%. These findings highlight a critical economic issue: The fact that so many phase 1 and phase 2 clinical trials fail in, or just prior to, phase 3 indicates that clinical trials in humans are often conducted using drugs that ultimately are proven to be nonefficacious or even to compromise health. High clinical trial failure rates are associated with enormous loss of financial resources, making drug discovery exorbitantly expensive for scientists, investors, consumers, and society.

In a 1929 paper in the journal Science (6), Nobel laureate August Krogh proposed the tantalizing potential contribution of naturally occurring diseases in animals as models of human disease; he articulated what later became known as Krogh’s principle: “For a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied” (6). This vision was realized more than 30 years later when clinical trials were conducted in client-owned dogs with naturally occurring cancer, and currently, clinical trials in pet dogs and cats are at the forefront of translational efforts to discover and develop new anticancer therapeutics (7). The valuable experience gained from canine cancer models has inspired other disciplines such as regenerative medicine and tissue
Organized academic veterinary medicine has also made dramatic advances over the past 20 years with the development of specialties, subspecialties, and advanced training that parallel the dramatic expansion of the specialties and subspecialties in human medicine. Currently, there are 22 veterinary clinical specialty organizations that are accredited by the American Board of Veterinary Specialties, with 28 subspecialties and 11,417 active specialists (Fig. 2). Entrepreneurial cross collaboration between and within universities, as well as between universities and biotechnology and pharmaceutical companies, is increasingly common and facilitates the highest standard of care. More and more, veterinary schools are becoming externally focused, with an eye to developing relationships with industry to accelerate the discovery and development of lead therapeutic compounds and devices and to conduct veterinary clinical trials. Where appropriate, naturally occurring diseases in companion animals may be incorporated into the FDA drug and device development process as a link between preclinical studies in laboratory animals and clinical trials in human patients. Doing so has the potential for providing robust efficacy data and improving the predictive value of preclinical studies (Fig. 1).

COMPARATIVE BIOMEDICINE
There is great variability in disease susceptibility among the various companion animals, which reflects differences in genetic background, physiology, lifestyle, and environment. Identification and optimization of the appropriate naturally occurring disease model for a given human disease target requires in-depth knowledge of comparative anatomy, physiology, pathology, and medicine. Here, we highlight several examples of naturally occurring diseases in companion animals that have major parallels to human disease (Fig. 3).

Cancer is common in dogs and accounts for almost 50% of all mortalities in dogs over 10 years old (7, 12). In the United States alone, there are more than 40 million new cases of cancer diagnosed in dogs each year, making canine cancer a statistically powerful model. Moreover, cancer is a complex, multifactorial disorder that develops over a long period of time prior to any clinical evidence of disease. These fundamental characteristics of disease complexity and progression contribute to the limited predictive value of traditional induced models of cancer in rodents. Comparative canine oncology and carcinogenesis have been extensively reviewed (7, 12), and in 2007, the Canine Comparative Oncology Genomics Consortium within the U.S. National Cancer Institute (NCI) was established. Since then, a robust and well-annotated biorepository of canine tissues has been established. Veterinary and human oncologists have partnered with basic cancer researchers to create the Comparative Oncology Trials Consortium within NCI, which functions to design and execute multi-institutional clinical trials in companion animals with spontaneous cancer as a means to evaluate and predict safety, efficacy, and identification of biomarkers or pharmacodynamic end points. Research into naturally occurring cancer in dogs and multidisciplinary collaboration is revealing new aspects of carcinogenesis and cancer biology (13–15), facilitating the development of new diagnostic methods (16), and enabling the translation of innovative personalized therapeutics to human clinical trials (17–19). Currently, there are 12 canine clinical trials registered in NCI’s Comparative Oncology Program that are investigating new therapeutics and diagnostic modalities for the benefit of canine and human patients alike.

According to the U.S. Centers for Disease Control and Prevention, an estimated 27 million U.S. adults suffer from osteoarthritis, a chronic and progressive musculoskeletal disorder that is often associated with articu-
The numbers of board-certified veterinary specialists and specialty organizations since 1950 (A) and the current distribution of veterinary specialists (B) are depicted. In 1951, the American College of Veterinary Pathologists was recognized as the first specialty organization. Since then, the American Veterinary Medical Association’s American Board of Veterinary Specialties has given accreditation to 21 additional specialty organizations. The most recent addition, the American College of Animal Welfare, was accredited in 2012. Congruous with the expansion of recognized specialties, the numbers of board-certified specialists is also on the rise. A small community of 389 veterinary specialists in the year 1967 has increased exponentially throughout the intervening years. At the time of this writing, there are more than 11,000 active board-certified veterinary specialists.
approaches such as gene therapy and therapeutic genome editing (29).

TRANSLATIONAL RECORD
The literature published in the veterinary field on naturally occurring diseases, including cutting-edge diagnostic techniques and innovative therapies, is on a rapidly rising trajectory and contains a plethora of knowledge that can inform the translational research community (8). Nonetheless, the fact that companion animals with naturally occurring diseases have proven to be clinically relevant translational models is only beginning to gain recognition in the broader biomedical community (8). Existing examples of successful translation of companion-animal models for therapy development most often have resulted from collaborations between veterinary and human clinician-scientists.

Keratoconjunctivitis sicca (KCS), or dry eye disease, is an ocular inflammatory disease in humans and dogs that affects ~7.1 million people in the United States over the age of 40. KCS is most commonly caused by immune-mediated destruction of the lacrimal gland leading to chronic corneal epithelium inflammation, pain, and, in severe cases, blindness (30, 31) (Fig. 3, B and b). Restasis is a cyclosporine-based ophthalmic emulsion that is widely used to treat KCS and was identified as a potential therapeutic for the treatment of human KCS after a veterinary ophthalmologist reported that topical cyclosporine was an effective therapy in dogs with naturally occurring KCS (32). This discovery paved the way for the successful translation from canine to human medicine. Subsequently, Lifitegrast, a topical immune-modulating agent, was proven efficacious in the treatment of canine KCS, a milestone that helped motivate entry into human clinical trials and reaffirm canine KCS as a powerful translational disease model (31).

Ibrutinib is an FDA-approved selective and covalent inhibitor of Bruton’s tyrosine kinase used for the treatment of mantle cell lymphoma and chronic lymphocytic leukemia. Naturally occurring non-Hodgkin’s lymphoma in dogs was chosen as a naturally occurring disease model, complementary to murine lymphoma models, during the preclinical development phase of ibrutinib (18). This trial in a naturally occurring B cell malignancy in dogs set the stage for accelerated FDA approval of the drug for use in human patients with mantle cell lymphoma (November 2013). This unusual approach was acknowledged in an article in Forbes: “In this case ... rather than force the molecules through traditional assays (and get a false negative result), they tried to use a less traditional approach (e.g. spontaneous lymphoma model in dog), and then proceed rapidly to the clinic.”

Naturally occurring osteosarcoma in client-owned dogs has helped optimize the preoperative and operative techniques for limb-sparing surgery currently used in pediatric and adult patients (33, 34). Osteosarcoma in dogs is also an outstanding model for therapy development, because tumor size in dogs is more relevant to human tumors than tumor size in rodents, which permits the adjustment of therapeutics and surgical devices for human applications.

Repairing critical size mandibular defects in dogs has received attention from the medical community and the general public (35, 36). Mandibular critical size defects result from trauma, cancer removal, or war-related injuries (Fig. 3, C and c). The use of recombinant human bone morphogenetic proteins (rhBMP) has been FDA approved for human spinal fusion products. The use of rhBMP-2 and a collagen-hydroxyapatite/tricalcium phosphate scaffold has been highly successful for bone regeneration in dogs (35, 36), and at the University of California, Davis’s Veterinary Medical Teaching Hospital, we have instituted this approach as a routine procedure for dogs in need of mandibular reconstruction. This dog model
may be instrumental in refining techniques, understanding the regenerative process, and providing valuable information on potential complications, thus paving the road toward solving this as-yet-intractable problem in humans.

Chronic inflammatory disorders are of particular interest because current treatments often rely on lifelong immunosuppressive therapy. Harnessing stem cell therapies for these disorders already occurs in human and veterinary medicine (37, 38). Mesenchymal stem cells (MSCs) have a regenerative ability attributed in part to their capacity to modulate both the innate and adaptive immune systems (39). Because of these attributes, MSCs are currently in phase 1–3 clinical trials for immune-mediated diseases, and parallel clinical trials are ongoing at veterinary schools across the nation. We have proposed feline chronic gingivostomatitis as a naturally occurring disease model of human chronic oral inflammatory diseases (including oral lichen planus, stomatitis, oral Crohn’s disease, and pemphigus) (40, 41). This prevalent naturally occurring disease permits optimization of cell dose, route of administration, and cell source, all of which can inform human clinical trials. The ability to study cellular therapy in the context of an intact immune system in a naturally occurring disease model is critical for early safety and efficacy studies.

Cardiovascular research and therapy is another field that could benefit from naturally occurring animal models. Cardiomyopathies are a major cause of morbidity and mortality in children and adults (Fig. 3, D and d). For inherited cardiomyopathies, therapeutic gene transfer holds great promise as a potential treatment. Several naturally occurring disease models, primarily in dogs and cats, offer excellent opportunities to evaluate new candidate therapies with the use of an adeno-associated viral vector for cardiac gene therapy (42, 43). Dogs and cats have a number of inherited cardiomyopathies, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (44–47). Therefore, collaborations between cardiovascular and gene-therapy researchers may illuminate treatments for human and veterinary patients.

**LIMITATIONS**

Whereas certain animal species share aspects of human genomics and physiology, all animal models have limitations, and the predictive value of results should always be interpreted cautiously. Moreover, although clinical trials in naturally occurring diseases of companion animals have the potential to inform human clinical trials, currently, many of the veterinary clinical trials are not being designed with an eye to inform human clinical trials and lack in several crucial features, such as statistical power, blinding, and appropriately sized control groups (48, 49). Another limitation is that no naturally occurring disease correlates in companion animals exist for several of the key diseases that are the cause of significant morbidity and mortality globally (for example, coronary heart disease, stroke, Parkinson’s disease, and monogenic genetic disorders such as thalassemia, sickle cell anemia, fragile X syndrome, and Huntington’s disease). Moreover, there are well-described differences in drug metabolism and genetic backgrounds between humans and all animal species, and idiosyncratic reactions and discrepant results will always play a role in translational research (50).

For example, after in vitro studies that demonstrated marked cytotoxic effects of a new acyclic nucleotide analog (GS-9219) in human lymphoblasts and human leukemia cell lines, the drug candidate was evaluated in dogs with naturally occurring, advanced-stage lymphoma. These studies established pharmacokinetics, safety parameters, and biological activities of the candidate drug, which displayed significant efficacy after a single administration with an acceptable adverse-event profile (51). Inspired by the results of rodent studies and canine clinical trials, phase 1 and 2 studies were initiated in humans with hematological malignancies. Although the drug showed acceptable levels of toxicity in mice and dogs, GS-9219 had

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**Table 1. Human diseases and their parallels in companion animals: A partial summary**

<table>
<thead>
<tr>
<th>Disease category or organ system</th>
<th>Specific disease</th>
<th>Species with recognized naturally occurring correlate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Dogs, cats</td>
<td>(7, 12)</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma</td>
<td>Dogs, cats</td>
<td>(7, 12)</td>
</tr>
<tr>
<td></td>
<td>Mammary carcinoma</td>
<td>Dogs, cats</td>
<td>(7, 12)</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>Dogs, cats</td>
<td>(7, 12)</td>
</tr>
<tr>
<td></td>
<td>Soft tissue sarcoma</td>
<td>Dogs, cats</td>
<td>(7, 12)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Chronic osteoarthritis</td>
<td>Dogs, horses, rabbits</td>
<td>(23, 53, 54)</td>
</tr>
<tr>
<td></td>
<td>Tendon injuries</td>
<td>Horses</td>
<td>(55)</td>
</tr>
<tr>
<td></td>
<td>Cruciate ligament injury</td>
<td>Dogs</td>
<td>(56)</td>
</tr>
<tr>
<td></td>
<td>Mandibular reconstruction</td>
<td>Dogs</td>
<td>(35, 36)</td>
</tr>
<tr>
<td>Spinal cord injury and disorders</td>
<td>Intervertebral disk herniation</td>
<td>Dogs</td>
<td>(27)</td>
</tr>
<tr>
<td></td>
<td>Neural tube defects</td>
<td>Dogs</td>
<td>(29)</td>
</tr>
<tr>
<td>Genetic</td>
<td>Hemophilia</td>
<td>Dogs</td>
<td>(57)</td>
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<td>Narcolepsy</td>
<td>Dogs</td>
<td>(58)</td>
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<td></td>
<td>SCID X-linked</td>
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<td>(59)</td>
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<td></td>
<td>Cleft palate</td>
<td>Dogs</td>
<td>(60)</td>
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<td>Duchenne muscular dystrophy</td>
<td>Dogs</td>
<td>(61)</td>
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<td>Lysosomal storage disease</td>
<td>Dogs, cats, cows, sheep goats</td>
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<tr>
<td></td>
<td>Skeletal disorders</td>
<td>Horses</td>
<td>(63)</td>
</tr>
<tr>
<td>Eye</td>
<td>Keratoconjunctivitis sicca</td>
<td>Dogs</td>
<td>(24)</td>
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<tr>
<td>Immune or inflammatory</td>
<td>Inflammatory bowel disease</td>
<td>Dogs, cats</td>
<td>(64, 65)</td>
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<tr>
<td></td>
<td>Chronic gingivostomatitis</td>
<td>Cats</td>
<td>(41)</td>
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<td>Cardiovascular</td>
<td>Dilated cardiomyopathy</td>
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<td></td>
<td>Hypertrophic cardiomyopathy</td>
<td>Cats</td>
<td>(44)</td>
</tr>
<tr>
<td></td>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>Dogs</td>
<td>(46)</td>
</tr>
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marked toxicity in human patients, and drug development was halted.

ETHICAL CONSIDERATIONS
Ethical considerations in veterinary clinical trials are fundamentally different from those of preclinical animal studies, in which the disease state is induced into animals by the investigator, and animals may be sacrificed at the end point of the study. Rather, we propose to study naturally occurring diseases in animals in which their owners are seeking veterinary care, in a parallel fashion to human clinical trials and the human health care system. This approach negates any induced animal distress, quelling public outcry, as research is being conducted in animals only after informed consent. These animals are housed by their owners and are not harmed in any way—on the contrary, these animals receive cutting-edge therapeutics for their diseases.

As in human clinical trials, ethical aspects need to be addressed to protect both animals and their owners. Much like clinical trials in children, sick animals are unable to accept or decline experimental treatment, and so their owners are entrusted to make these decisions on their behalf and to provide legal guardianship. The American Veterinary Medical Association (AVMA) supports clinical studies and therapy directed at naturally occurring diseases in animals with a goal to inform human medical issues (52). In this regard, each study should be reviewed at the institutional level either by the Institutional Animal Care and Use Committee (IACUC), a Clinical Trials Review Board, or a combination of such committees to ensure thorough scientific and ethical review. Informed and signed owner consent should be obtained only after reviewing all available diagnostic and standard treatment options, along with associated risks, benefits, and likely prognoses. To avoid complex bias issues, consent ideally should be obtained by someone other than the primary investigator who has no conflict of interest. Furthermore, as in human clinical trials, economically challenged pet owners should not be exploited, and all possible standard-of-care treatment options should be available to their pets prior to enrolling in a clinical trial.

GALLOPING FORWARD
In order to break down physical and conceptual barriers that impede productive interactions between academic scientists and clinicians in veterinary schools and academic medical centers as well as industry and regulatory scientists, we propose a roadmap to facilitate dissemination of knowledge, encourage cross-disciplinary collaboration, and build the required infrastructure.

Identify naturally occurring diseases with potential for accelerating translation. Expert panels of physicians, veterinarians, and researchers should be formed to (i) critically evaluate the similarities between human disease and related spontaneous diseases present in companion animals (disease phenotype, similarities in biomarkers, and response to current therapeutics) and (ii) determine the feasibility of conducting veterinary trials to evaluate new therapeutics and devices based on veterinary patient databases.

Create opportunities for synergistic clinical education. Medical and veterinary medical schools should create strategic teams that will develop ways by which students, residents, and faculty members can have increased opportunities for cross-disciplinary interactions. These may include incorporation of comparative medicine material into the curriculum [One Health Initiative: http://www.onehealthinitiative.com], cross-disciplinary teaching opportunities for faculty members, and comparative-medicine training opportunities for clinical residents and students. Postgraduate fellowships can be an extraordinary opportunity for medical and veterinary residents to attain an intimate and in-depth appreciation of the other discipline's challenges, needs, and strengths, thus promoting true cross-disciplinary collaboration. Knight's Landing's One Health combined veterinary and human clinic in California is one example of such an endeavor that illustrates the benefits for medical and veterinary professionals and the two- and four-legged community members.

Create platforms for fusing graduate education with clinical studies. Interactions between graduate and professional students in the health sciences could include seminars, workshops, and summer projects that highlight comparative and translational medicine. Dual-degree DVM-Ph.D. training programs are already being offered at some institutions, and postgraduate research training fellowships and career development awards are solicited by the U.S. National Institutes of Health (NIH).

Create interdisciplinary platforms to facilitate dissemination of translational concepts. The creation and support of professional societies, symposia, and high-tier journals that are dedicated to translational medicine research are instrumental for the review and wide dissemination of cutting-edge knowledge. Many such symposia already exist and include the integrated human and veterinary aerodigestive team symposium, the joint human and veterinary cardiology symposium, and the zoobiquity conference. These team symposia are excellent forums for developing collaborations and engaging colleagues outside of their disciplinary community.

Divert resources to support translational medicine research efforts. Many of the barriers to true cross-disciplinary building to emphasize relevant naturally occurring animal models of disease involve the availability of resources. Universities are typically conservative and risk-averse when it comes to intellectual property and conflicts of interest. However, as state financial support of universities diminishes, many entrepreneurial activities that involve deep collaborations with scientists outside the university are being managed and encouraged. Entities within the universities are supporting outreach to companies and promoting industry partnerships (through research garage space and “soft nests” for clinician research). As such, there is far more clarity regarding collaborative science and how clinician-scientists can serve a role in a contract research organization.

Inspired by the Comparative Oncology Program within NCI, we recommend that parallel translationally oriented programs within NIH be tasked to facilitate the execution of multi-institutional companion animal clinical trials that include physicians, scientists, and veterinarians; generate tissue banks; and create granting mechanisms. Ideally, a national center would coordinate (i) multicenter trials required to accelerate enrollment of appropriate patients, (ii) education of veterinary students, hospital staff, and clinician-scientists to foster a culture of clinical trials, and (iii) collection and analysis of data related to trial costs, time to market, and trial successes and failures.

Clinical trials involving companion animals are expensive compared to rodent models. However, many of the costs to determine if the patient is eligible for enrollment or not need long-term housing. Pet owners are
eager to enroll in clinical trials and engage with faculty at academic institutions. Time is perhaps the most valuable resource: It takes time and effort to build research teams that can articulate and create opportunities and acquire funding for the development of relevant animal models.

Consensus statement. Last, we recommend that a consensus statement regarding the trajectory for veterinary clinical trials in translational medicine be published by a group of leading clinicians and scientists to inform the translational research community regarding the extramural funding opportunities, opportunities for collaboration, and study-design and study-report standards for veterinary clinical trials. The U.S. National Academy of Medicine convened a meeting in June 2015 to generate such a consensus statement regarding veterinary clinical trials in oncology (“The role of clinical studies for pets with naturally occurring tumors in translational cancer research”; http://iom.nationalacademies.org/Activities/Disease/NCPPF/2015-JUN-08).

REFERENCES AND NOTES


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