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Precision Wildlife Medicine: Applications of the Human-centred Precision Medicine Revolution to Species Conservation

Jenny Whilde[1], Mark Q. Martindale[1] and David J. Duffy[1, 2]

[2]Systems Biology Ireland, Science Link Building, University College Dublin, Belfield, Dublin 4, Ireland.

[1]The Whitney Laboratory for Marine Bioscience & Sea Turtle Hospital, University of Florida, 9505 Ocean Shore Blvd. St. Augustine, FL 32080-8610, USA.

Correspondence to: David J. Duffy. Email: duffy@whitney.ufl.edu.

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Abstract

The current species extinction crisis is being exacerbated by an increased rate of emergence of epizootic disease. Human-induced factors including habitat degradation, loss of biodiversity, and wildlife population reductions resulting in reduced genetic variation are accelerating epizootic disease emergence. Novel, efficient and effective approaches are required to combat these epizootic events. Here, we present the case for the application of human precision medicine approaches to wildlife medicine in order to enhance species conservation efforts. We consider how the precision medicine revolution, coupled with the

advances made in genomics, may provide a powerful and feasible approach to identifying and treating wildlife diseases in a targeted, effective and streamlined manner. A number of case studies of threatened species are presented which demonstrate the applicability of precision medicine to wildlife conservation, including sea turtles, amphibians and Tasmanian devils. These examples show how species conservation could be improved by using precision medicine techniques to determine novel treatments and management strategies for the specific medical conditions hampering efforts to restore population levels. Additionally, a precision medicine approach to wildlife health has in turn the potential to provide deeper insights into human health and the possibility of stemming and alleviating the impacts of zoonotic diseases. The integration of the currently emerging Precision Medicine Initiative with the concepts of EcoHealth (aiming for sustainable health of people, animals, and ecosystems through transdisciplinary action-research) and One Health (recognising the intimate connection of humans, animal, and ecosystem health and addressing a wide range of risks at the animal–human–ecosystem interface through a coordinated, collaborative, interdisciplinary approach) has great potential to deliver a deeper and broader interdisciplinary-based understanding of both wildlife and human diseases.

Precision medicine in human healthcare

To appreciate the potential for precision wildlife medicine to enhance species conservation efforts, one must first consider how precision medicine approaches are improving human healthcare. Precision medicine can be defined as treatments targeted to the needs of disease groups on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics (Jameson & Longo, 2015). This rapidly emerging field is revolutionizing our understanding of disease, drug development and repurposing, human patient care and treatment decisions by emphasising disease prevention and tailoring precision treatments targeted to stratified patient

cohorts or even individual patients (Byron *et al.*, 2016, CASyM Consortium, 2014, Collins & Varmus, 2015, Committee on a Framework for Developing a new Taxonomy of Disease, 2011, Duffy, 2016, Duffy *et al.*, 2015, Flores *et al.*, 2013, Hood & Friend, 2011, Vandamme *et al.*, 2013). Precision medicine incorporates a number of new technologies (Table 1) with advanced computational analysis (Duffy, 2016) to improve our understanding of disease and predict in advance the response of disease groups and individual patients to therapy. Furthermore, these technological advances are elucidating previously intractable disease mechanisms, fundamentally altering our ability to detect and treat diseases, and enabling us to respond to emerging diseases at an unprecedented rate.

Thanks to these advances, our response to viral outbreaks has never been more rapid. For instance, technological improvements, starting with the ability to rapidly sequence viral genomes, led to the swift development of vaccines for the recent human Ebola outbreak (see Wildlife Case Study 3 below (Gire *et al.*, 2014)). Similarly, precision medicine approaches are greatly advancing our understanding of and our ability to detect and tackle the emerging Zika virus. Again, the strain of Zika virus responsible for the current Americas epidemic was rapidly sequenced using next-generation sequencing technology (Enfissi *et al.*, 2016), with the sequenced Zika viral genome speeding our ability to respond to the outbreak. Amazingly, based on the sequenced genome a team of researchers was then able to develop and manufacture a prototype inexpensive paper-based field test for Zika in just five days (Pardee *et al.*, 2016). This diagnostic test requires only a small blood sample from a patient and provides results within three hours. As was the case with the recent Ebola outbreak, thanks to technological advances rapid progress is being made towards the development of a Zika vaccine (Larocca *et al.*, 2016).

Precision medicine approaches are also revolutionising our ability to diagnose inherited and chronic diseases. For example, next-generation sequencing technologies are facilitating the

non-invasive diagnosis of foetal chromosomal abnormalities which can lead to genetic disorders, including Down syndrome (Bianchi, 2012, Bianchi *et al.*, 2014, Palomaki *et al.*, 2011). This approach detects foetal DNA fragments circulating in maternal blood, and is sensitive enough to be more accurate than traditional tests, while avoiding any invasive testing of the foetus itself.

The field of oncology is pioneering precision medicine for detection and monitoring of cancers, identifying the drivers of cancers and accurately stratifying patients for targeted treatments. The ability to characterise tumour genomes and use that information to develop effective drug treatment plans tailored to the individual is revolutionising oncology (Ciardiello *et al.*, 2014, Garraway *et al.*, 2013). Lung cancer patients now routinely have their tumours sequenced to identify the specific gene mutations driving an individual patient's tumours. Only once the mutation has been identified is the patient started on a tailored chemotherapy regimen, ensuring the right drug for the right patient (Mirnezami *et al.*, 2012, Saito *et al.*, 2016, Vargas & Harris, 2016). This approach results in dramatically improved response rates of up to 94%, over a previous one-size-fits-all approach in which only 10% of patients responded to chemotherapy (Mirnezami *et al.*, 2012; Shea *et al.*, 2016). As with genetic disorders, sequencing-based assays are also being developed to harness cell-free DNA circulating in patient blood samples to diagnose cancer, predict relapse and segregate patients for targeted therapies (Rapisuwon *et al.*, 2016, Schwarzenbach *et al.*, 2011, Tie *et al.*, 2016).

The emergence of precision medicine has been driven by an unprecedented ability to generate and analyse big data, and by the convergence of omics technologies (Table 1), the computational revolution, medical and research knowledge-bases, and advances in bioinformatics and mathematical modelling (Castagnino *et al.*, 2016, CASyM Consortium, 2014, Committee on a Framework for Developing a new Taxonomy of Disease, 2011, Duffy,

2016, Flores *et al.*, 2013, Hood & Friend, 2011, Parodi *et al.*, 2016, Robinson, 2012, Tortolina *et al.*, 2015, Vandamme *et al.*, 2013). While every one of these factors is not necessarily required for each precision medicine project, the interchangeable combination of these factors is facilitating our most in-depth understanding of human health and disease to date. Precision medicine is not only driving rapid advancements in the understanding and treatment of previously intractable disease, but can also dramatically reduce the time required to progress the treatment of novel emerging diseases.

Table 1. Selected omic approaches and their relevant technologies.

Omic technology	Approach	Primary technology used
Genomics	Global study of DNA	Next-generation sequencing
Proteomics	Global study of proteins	Mass spectrometry
Transcriptomics	Global study of RNA	Next-generation sequencing
Metabolomics	Global study of metabolites	Mass spectrometry
Glycomics	Global study of carbohydrates	Mass spectrometry
Lipomics	Global study of lipids	Mass spectrometry
High-throughput imaging	Computationally assisted image analysis	Various
High-throughput drug screening	Large scale simultaneous drug screens on animal cells	HTS robotics

Harnessing the potential of precision medicine to tackle emerging wildlife disease

The exponential growth of the precision medicine approach in human healthcare, and the increasingly widespread application of modern diagnostic tools (Pokorska-Bocci *et al.*, 2014) indicate an equally powerful potential for rapid advances to be made in veterinary and wildlife medicine if such approaches are adopted by these disciplines (Fig. 1). While habitat degradation and pollution are major contributors to exacerbating and hastening species loss, pathogens can severely affect the success of wildlife populations, and, when combined with other detrimental issues such as habitat loss and climate change, can contribute to local and global extinctions (Brearley *et al.*, 2013, Burge *et al.*, 2014, Maxwell *et al.*, 2016; Smith *et al.*, 2009). It has been calculated that as the risk of extinction of a species increases, so, too, does the effect of diseases on the population of that species (Heard *et al.*, 2013), and a number of endangered species are currently under threat from diseases that are spreading

unchecked through their populations. Therefore, the most highly endangered species have greatest need of rapid, effective disease treatment.

There are dramatic and often unpredictable knock-on effects of the loss of a single species to disease on the surrounding ecosystem (Hollings *et al.*, 2014). These factors, coupled with the increased rate of emerging diseases in the wild as a consequence of human-induced habitat degradation and destruction (Daszak *et al.*, 2000, Daszak *et al.*, 2001, Lamb & Willis, 2011), highlights the urgency and necessity of applying precision medicine to conservation and wildlife diseases. Understanding, treating and preventing wildlife diseases is important not only for the health of individual animals but also more generally for the conservation of entire species and the broader ramifications of species decline and loss on the wider biome. Wildlife medicine faces many well-recognised challenges, including the difficulty of obtaining samples from wild populations, and a lack of surveillance of wildlife populations resulting in delayed awareness of outbreaks and epidemics. Lack of information on the number of individuals at risk can make it difficult to determine disease prevalence (Martineau *et al.*, 2002). Resources may be limited for monitoring and testing wildlife health, and diagnostic techniques that are currently used for humans may be unavailable or not applicable to other species (McAloose & Newton, 2009). Small sample sizes are frequently a problem in wildlife medicine, whether because of the difficulty of obtaining multiple samples in the natural environment (Dudgeon & Ovenden, 2015), because the numbers of an endangered species are critically low, or the species is elusive (Waits & Paetkau, 2005).

Data-driven omics approaches (genomics, proteomics, transcriptomics, phenomics, metabolomics, etc.) harnessed and interpreted by precision medicine's high-end computational approaches (Duffy, 2016, Jameson & Longo, 2015, Lander, 2016) are extremely relevant to the field of conservation medicine as they extract the maximum amount of information possible from a given sample, which is particularly important when dealing

with rare or irreplaceable samples. Because omic approaches generally rely on mass spectrometry or next-generation sequencing, they do not require the development of species-specific diagnostic tests. Once molecules are extracted from a sample (e.g. DNA, RNA or protein) the subsequent work-flows for such technologies are identical regardless of the source organism. Indeed, these technologies can simultaneously identify molecules from multiple organisms within the same sample, e.g. all viral, bacterial and eukaryotic DNA present in a blood sample. Furthermore, due to the initially prohibitive costs of these technologies, even for human research, the analysis methodologies associated with these technologies have been specially designed to cope with small sample sizes (Gadbury, 2004).

By avoiding the iterative hypothesis-driven process of classical approaches to disease investigation, precision medicine enables more rapid discovery. These rich datasets provide a means to make data-driven hypotheses which can then be reassessed using additional computational approaches to re-interrogate existing datasets without being critically limited by the availability of additional samples.

The advent of genomic technologies is also revolutionising the field of species and disease monitoring. While wildlife monitoring has traditionally relied on physical identification of species by visual surveys and counting of individuals, genomics- and qPCR-based environmental DNA (eDNA) approaches are rapidly and fundamentally altering monitoring activities (Bohmann *et al.*, 2014, Thomsen & Willerslev, 2015). Environmental DNA is an efficient, non-invasive and easy-to-standardize sampling approach which can be coupled with sensitive, cost-efficient and ever-advancing DNA sequencing technology to detect species-specific DNA fragments shed into the environment (Thomsen & Willerslev, 2015). The combination of eDNA and precision medicine approaches will facilitate all aspects of disease management, from surveillance to treatment discovery, therapy and management implementation, and long-term monitoring of the effects of interventions across a population.

This type of technology also contributes to our understanding of pathogen behaviour – for example, eDNA has been used to determine how long *Batrachochytrium dendrobatidis*, a key cause of amphibian population decimation, survives outside its host (Walker *et al.*, 2007) (see Wildlife Case Study 5). Interestingly, precision medicine approaches can also be applied to retrospectively understanding disease cause and spread, providing further valuable resources to combatting wildlife disease. For example, the complete viral genome of phocine distemper virus from a 1988 outbreak in harbour seals was isolated from a 25-year-old sample (de Vries *et al.*, 2013).

The selected case studies examined below show specific examples of the applicability of genomic and precision medicine approaches to wildlife conservation and demonstrate the importance of it being adopted more widely by the conservation community. These case studies serve as informative examples, representing a small subset of the many prominent examples of epizootic events which occur across the animal kingdom, from invertebrates to mammals (Aeby *et al.*, 2011, Bodewes *et al.*, 2013, Brearley *et al.*, 2013, Daszak *et al.*, 2001, Di Guardo & Mazzariol, 2016, Foley *et al.*, 2011, Masahito *et al.*, 1988, Metzger *et al.*, 2015, Vega Thurber *et al.*, 2014). The presented case studies include both examples where no precision medicine approaches have thus far been applied and cases where precision medicine approaches are already enhancing our understanding of and treatment options for the disease.

Wildlife Disease Case Study 1: Fibropapillomatosis in sea turtles

Fibropapilloma (FP) tumours have become panzootic in green sea turtles *(Chelonia mydas)* in recent years (Williams *et al.*, 1994). This primarily external cancer (Fig. 2) is undermining turtle conservation efforts globally. Fibropapilloma tumor occurrence is thought to be linked

to the combination of herpes virus infection (Page-Karjian *et al.*, 2015) and local human-induced habitat degradation (dos Santos *et al.*, 2010, Jones *et al.*, 2016). Although generally not malignant, tumors can be fatal, restricting turtles' feeding, swimming, reproduction and vision and causing immunosuppression. While green turtle populations in some areas are thriving (Broderick *et al.*, 2006, Derville *et al.*, 2015), FP is now spreading to more northern latitudes where it has never been previously recorded (Duarte *et al.*, 2012, Foley *et al.*, 2007, Hirama & Ehrhart, 2007, Metz *et al.*, 2014, Page-Karjian *et al.*, 2014), which may be indicative of more widespread problems in the marine environment. The FP-associated herpesvirus has previously been identified in non-FP bearing populations, which suggests that the current widespread geographic emergence of FP is being triggered by rising ocean temperatures brought about by human-induced global warming and environmental contaminants, rather than altered infection rates (Aguirre & Lutz, 2004, Jones *et al.*, 2016, Page-Karjian *et al.*, 2012). The only commonly applied treatment for FP is surgery, which is expensive and restricted to a small number of turtle hospitals. Additionally, 60% of tumours regrow post-surgery (Page-Karjian *et al.*, 2014), necessitating longer periods of rehabilitation and additional rounds of surgery. Since these records are only for the relatively short period of hospitalization, it is likely that the true occurrence of tumour regrowth with current treatment techniques is much higher. Furthermore, there is currently no treatment for turtles presenting with internal tumors, with such turtles being euthanized.

We have recently instigated the use of cutting-edge tumour profiling and computational analysis techniques that are currently used in human oncology (Duffy, 2016) to identify novel therapeutic options to turtles with FP. By profiling the global activity status of all of the turtle and viral genes being expressed in healthy tissue and FP tumours across multiple stages, using deep sequencing-based transcriptomics, we can determine the oncogenic events driving tumour formation and progression. By computationally integrating this data at the pathway,

gene ontology and inferred regulator level, using approaches validated for human cancers (Duffy, 2016, Duffy *et al.*, 2015), we can reconstruct the oncogenic signalling and effector networks promoting tumour growth. This approach not only identifies the relevant regulators and pathways but computationally infers their degree of activation or inhibition, by collating the changes in the expression of their target genes. Once reconstructed, these networks can be used to identify vulnerabilities (key oncogenic network components) which are targetable using existing anti-cancer therapeutics. From the therapeutics identified by these approaches, we will prioritise the use of longer-established, cheaper compounds from the large back catalogue of FDA-approved drugs, over more recent and prohibitively expensive 'designer drugs'. It is anticipated that this approach will improve survivorship of FP-afflicted turtles. This is also a proof-of-principal test case to demonstrate the potential for precision medicine approaches to be used by the conservation and rehabilitation communities to rapidly advance the rate at which emerging wildlife disease can be tackled. We expect that vulnerabilities in FP tumours can be targeted by treating turtles with existing human anti-cancer drugs, at the numerous sea turtle rehabilitation facilities around the globe**.**

Wildlife Disease Case Study 2: Tumours in beluga whales

As with the environmental contribution to the development of FP in sea turtles (see Wildlife Disease Case Study 1), pollution has had a major impact on the beluga whale (*Delphinapterus leucas*) population of the St. Laurence Estuary (SLE), a population which suffers extensively from environmentally-linked cancers, specifically cancer of the proximal intestine (Martineau *et al.*, 2002). Although hunting has not been a threat to beluga whales since the 1980s (Martineau *et al.*, 2002), the population did not recover once that threat was removed, and further investigation found that cancer now appears to be a major contributor to beluga whale mortality, with 23% of beach-cast carcasses having malignant cancers

(Kingsley, 2002, Lair *et al.*, 2016). In fact, the beluga whale population in the St. Lawrence Estuary (SLE) in Canada exhibited cancer rates similar to that of humans and higher than that of any other population of wild terrestrial or aquatic animals (Martineau *et al.*, 2002). At the time of the aforementioned study (Martineau *et al.* 2002), only 33 individual cases of cancer, all of different types to that seen in the beluga whales, had been reported worldwide in captive and wild cetaceans other than SLE belugas. The type of cancer observed in the beluga whales, combined with environmental evidence of contamination means it is highly likely that the cancer prevalence in the SLE beluga was caused by environmental contamination by polycyclic aromatic hydrocarbons (PAHs) produced by local aluminium smelters (Martineau *et al.*, 2002). Polycyclic aromatic hydrocarbons can be highly toxic and carcinogenic to all life forms, from micro-organisms to humans and are formed during the incomplete burning of coal, oil, gas, wood and garbage (Samanta *et al.*, 2002, U.S. Department of Health and Human Services, 1995). While it would be preferable for PAHs and similar toxins to be prevented from entering the environment at all, the fact remains that the onus is on humans to either enact relevant environmental protection legislation or to develop treatments for species affected by such pollution. Precision medicine approaches would not only identify the specific effects of pollutants such as PAHs on the development of tumours, but precision approaches can also be used to develop targeted treatments that can potentially be applied to affected individuals, be they whales, turtles or humans. Precision medicine also has the potential to use omics techniques to identify gene signatures linked with environmental pollutants and cell-free circulating DNA tumour biomarkers from blood samples to assist monitoring. Interestingly, methods for obtaining biopsies from free-swimming humpback whales have recently been developed (Burkard *et al.*, 2015). Clear identification of the causes or triggers of cancer and other diseases in wildlife, and indeed human carcinogens that are released into the environment, will provide a strong and clear message to policy makers and

stakeholders about the importance of reducing pollution and restoring environmentally degraded areas, and may lead to public health interventions and the development of policy initiatives (Reif, 2011).

Wildlife Disease Case Study 3: Ebola virus in African great apes.

Ebola virus (EBOV) in humans is highly virulent and a significant bioterrorism threat. It also threatens critically endangered great apes; Western gorillas (*Gorilla gorilla*) were moved from 'endangered' to 'critically endangered' on the IUCN Red List of Threatened Species in 2007 because the population had declined by a third in 15 years due to this virus (Hopkin, 2007). Understanding the epidemiology and ecology of Ebola virus was a huge challenge for public health and scientific communities (Muyembe-Tamfum *et al.*, 2012), although fruit bats have been implicated as natural reservoir hosts (Gonzalez *et al.*, 2013). Recovered ape carcasses were infected by a variety of Ebola strains, suggesting that Ebola outbreaks in great apes result from multiple virus introductions from the natural host (Leroy *et al.*, 2005, Pourrut *et al.*, 2005). Surveillance of animal mortality may help to predict and prevent human Ebola outbreaks (Leroy *et al.*, 2004).

A precision medicine approach was implemented when the 2014 human Ebola outbreak occurred. The first step to tackling the epidemic and facilitating vaccine development was to conduct genomic surveillance of the virus, with 99 Ebola virus genomes being sequenced (Gire *et al.*, 2014). Successful EBOV vaccine candidates were then identified in preclinical studies and gene-based EBOV vaccines have been found to be immunogenic in human clinical trials. An ideal EBOV vaccine will give rapid and durable immunity against multiple EBOV strains. The sequencing of virus genomes in apes would facilitate the development of specific vaccines against multiple strains of viruses. Precision medicine approaches facilitate

the targeting of sequenced strains, as well as predicting whether existing human vaccines were likely to be beneficial to ape populations. Hoffmann *et al*. (2008) argue that there is strong justification to trial vaccines on great apes, and the impact on a few animals would be of great benefit to the ape population as a whole.

Wildlife Disease Case Study 4: Tasmanian devil facial tumour disease

Devil facial tumour disease (DFTD) is an emergent transmissible lethal cancer exclusive to Tasmanian devils (*Sarcophilus harrisii*) and is threatening the species with extinction in the wild (Pye *et al.*, 2016). Recently genomic-approaches have been brought to bear on DFTD (Deakin & Belov, 2012, Grueber *et al.*, 2015, Pye *et al.*, 2016). Devil facial tumour disease results in an extremely high rate of adult fatalities, with some wild populations already having been reduced by 95% (Deakin & Belov, 2012). Directly transmissible cancers, in which the pathogen is a clonal infectious cell line originating in a single individual and then spread through injurious contact, were considered to be extremely rare in nature (Ostrander *et al.*, 2016, Welsh, 2011). The recent discovery of a second, histologically different form of DFTD, known as DFT2, therefore suggests that either Tasmanian devils are particularly prone to this kind of disease, or that transmissible cancers are more prevalent in the wild than had been previously thought (Pye *et al.*, 2016). Recently, other such directly transmissible cancers have been discovered in shellfish, enabled by genomics approaches (Metzger *et al.*, 2015, Metzger *et al.*, 2016), bolstering the suggestion that transmissible cancers are actually more common in the wild than formerly believed. When DFTD cells have been transmitted from one devil to another, they appear to develop into a cancer without inducing an immune response. Both DFTD and canine transmissible venereal tumour (CTVT, a transmissible cancer in dogs (Frank, 2007, Murgia *et al.*, 2006)) have evolved mechanisms of immune

escape in allogeneic hosts, in part via epigenetic downregulation of major histocompatibility complex (MHC) gene expression in tumour cells. Reduced genetic diversity and the production of immunosuppressive cytokines may also contribute (Woods *et al.*, 2015). However, unlike DFTD, most cases of CTVT are eventually rejected by the host dog, which then is conferred lifelong immunity (Welsh, 2011). Human-to-human transmissible cancers occur very rarely. Only 16% of all cancers worldwide are due to infectious etiologies and the vast majority of these are through viral, bacterial or parasitic communicable infections, with only rare instances of human-human transmission occurring, usually during organ/stem cell transplantations or during pregnancy (de Martel *et al.*, 2012, Welsh, 2011).

There is an important role for tumour genetics to play in the understanding of DFTD transmission dynamics and epidemic outcome (Hamede *et al.*, 2015). The sequencing of the Tasmanian devil genome and its tumours not only provided a greater understanding of the etiology of the disease, it explained the dynamics of the spread of the disease (Murchison *et al.*, 2012), valuable information for those working to curtail DFTD and prevent further decimation of the Tasmanian devil population. Additionally, the insights gained from this genomic work have led to an ongoing vaccine trial, although vaccine efficiency may be complicated by the recent identification of the second form of DFTD. This type of precision genomic research provides a more accurate and faster method of understanding the evolution of host and pathogen genotypes, their effects on susceptibility, and tolerance to infection than would be possible using traditional methods. A better understanding of how such diseases emerge and are transmitted forms a foundation for designing novel genetic management strategies that facilitate disease management without negatively impacting diversity or adversely interfering with natural selection, and allows appropriate treatment to be promptly implemented.

Wildlife Disease Case Study 5: Chytridiomycosis in amphibians

Amphibian populations are declining at an unprecedented rate worldwide. A number of declines have been linked to a pathogenic skin fungus, *Batrachochytrium dendrobatidis* (Hernández *et al.*, 2014, Pereira *et al.*, 2013), which causes the development of a lethal skin disease, chytridiomycosis, which is now considered to be one of the greatest threats to biodiversity (James *et al.*, 2015). Immunity to this disease is becoming better understood in a laboratory setting (Ramsey *et al.*, 2010), but amphibian populations continue to be decimated. Six Australian species are now considered extinct, with seven more being under severe threat (Skerratt *et al.*, 2016). Skerratt *et al*. (2016) recognise that the effectiveness of novel management solutions will probably differ among species due to variation in disease ecology, and they emphasise the need for species-specific research. Additionally, a recently-discovered chytrid fungal pathogen from Asia, *Batrachochytrium salamandrivorans* (*Bsal*), which is specific to salamanders, could lead to rapid epizootic declines and extinctions in salamander fauna in North America, should the pathogen be inadvertently introduced (Yap *et al.*, 2015).

Precision medicine and genomic approaches have been applied to exploit the fact that while some amphibian populations are being decimated by *B. dendrobatidis*, some species are apparently unaffected. Differential gene expression tests and co-expression network analyses have shown that resistant species have reduced skin inflammatory responses and increased expression of genes involved in skin integrity, showing that resistance to chytridiomycosis may be related to a species' ability to escape the immunosuppressive activity of the fungus (Ellison *et al.*, 2015). Further omics techniques have been used to develop *in silico* models to link bacterial community structure with bacterial defensive function to help identify bacterial species involved in pathogen inhibition (Rebollar *et al.*, 2016). Whole microbiome sequencing, targeted 16S rRNA gene amplicon sequencing and other methods such as

indicator species analysis, the K-S Measure, and co-occurrence networks are recommended to identify bacteria that are associated with pathogen resistance in field surveys and experimental trials, thus providing a way forward in stemming mass extinctions of amphibians (Rebollar *et al.*, 2016). Precision medicine has been shown to have the capacity for improving biomarker development and assess a diverse array of biomarkers, including those based on gene transcriptional signatures, miRNAs, genes and peptides (Gonzalez de Castro *et al.*, 2013, Hamburg & Collins 2010). Barcoding of DNA is also being used in conservation efforts as a method of identifying cryptic diversity in amphibian communities (Crawford *et al.*, 2013), which will further contribute to understanding resistance and susceptibility to widespread diseases. Approaching wildlife diseases from two angles – examining both the susceptible, vulnerable populations, and those that appear to be less affected (James *et al.*, 2015) – using powerful modern techniques will further enhance our understanding of disease processes and indicate appropriate targeted strategies for treatment and mitigation. Chytridiomycosis is therefore another example of a wildlife disease which has benefited from the application of genomic approaches, although more work is needed to stem chytridiomycosis-associated amphibian extinctions.

Role of *ex situ* conservation facilities, such as zoos and wildlife rehabilitation centres, in precision wildlife medicine

It is feasible to apply precision medicine techniques to many wild-ranging species. Indeed, most omic approaches are already amenable to the analysis of field-collected samples. For instance, small samples (hair, skin, blood, etc.) are sufficient for genomics with field collection protocols already widely used by population genetics and environmental DNA studies (Creer *et al.*, 2016, DeSalle & Amato, 2004). Similarly, RNA for transcriptomics can be readily collected and transported through the use of existing RNA stabilisation reagents,

such as RNAlater (Qiagen). Field-based protein desiccation techniques for proteomic analysis have also been established (Roskens *et al.*, 2010). While field-based studies are feasible, the fullest implementation of precision wildlife medicine is best achieved by partnering with *ex situ* conservation facilities, such as zoos and wildlife rehabilitation centres.

Zoos conduct a number of activities which already lend themselves to the full development of precision wildlife medicine, such as active disease surveillance of collection animals as part of their routine preventative medicine programs, and the importance of monitoring the health and welfare of individual animals is well recognised (Hosey *et al.*, 2013). Zoos and other *ex situ* conservation facilities may also maintain serum and tissue banks as well as detailed medical records, and have staff with technical expertise in wildlife health. The Zoo Animal Health Network in the USA, for example, is a collaborative program with the United States Department of Agriculture that is involved in early disease detection and outbreak response programs. Animal health legislation is strictly applied to animals being transported in order to reduce the risk of disease transmission, as well as to safeguard wild populations. Zoos are often also involved in *in situ* conservation efforts, and the expertise and resources that zoos can offer to wildlife medicine are invaluable. In Australia, wildlife hospitals operated by the major zoos also treat a significant caseload of free-ranging and rehabilitation wildlife, and a zoo-based wildlife disease surveillance program has been developed to incorporate disease information from free-ranging wildlife into the existing national wildlife health information system (Cox-Witton *et al.*, 2014).

Because zoos keep records of each individual animal, it would be helpful to not only apply precision medicine to zoo-housed animals, but to look to zoos to develop precision disease management strategies that can be applied to animals in the wild, particularly large terrestrial vertebrates which are individually more readily identifiable initially, and can also be tagged

and tracked in the wild after treatment. Once a treatment has been devised, more inventive approaches to population-level treatments may be developed. For instance, to protect black-footed ferrets from sylvatic plague, the US Fish and Wildlife Service is trialling the aerial dispersal of vaccine-laced sweets (M&Ms) across the ferrets' habitat using a modified drone (McCollister & Matchett, 2016). Similarly, with the aim of inoculating European badgers against tuberculosis, researchers are searching for attractant flavours which would encourage badgers to eat pellets containing oral vaccine (Kelly *et al.*, 2011).

The information gleaned from genomic studies can be extremely valuable in understanding genome diversity within a single species. It is predicted that genomics will therefore contribute to determining which parts of a species' genomes are responsible for local adaptation and are therefore most important for zoos to preserve (McMahon *et al.*, 2014). Increased collaboration between *ex situ* conservation facilities and wildlife managers, and increased availability of facilities such as the zoo-based wildlife hospitals in Australia to wildlife researchers will undoubtedly increase the rate of understanding of wildlife diseases and effectiveness of treatment strategies.

Comparative analysis of cancer in large, long-lived species

The majority of the case studies presented here focus on emerging oncological threats to wildlife, as the field of human oncology is most rapidly embracing precision medicine (Ciardiello *et al.*, 2014, Garraway *et al.*, 2013) and therefore has developed the most advanced tools and techniques. Additionally, increased study of wildlife cancers can greatly progress our understanding of human tumours. It has been established that longer-lived species tend to be more cancer resistant than their short-lived counterparts that lack robust anti-cancer defences (Greaves & Ermini, 2015). For example, African elephants (*Loxodonta*

africana) are relatively cancer resistant compared with humans, having a cancer mortality of 4.81% while humans have a cancer mortality rate of 11-25%. A recent study has shown that this is in fact likely to be due to the fact that elephants possess multiple copies of the *TP53* (p53) tumour suppressor gene, and elephant cells demonstrate an increased p53-mediated apoptotic response following DNA damage compared with human cells (Abegglen *et al.*, 2015). Genomic studies of other large species would determine whether lower cancer rates can be attributed to genomic differences or to natural mechanisms that exist in larger species to suppress cancer (Caulin & Maley, 2011). These insights may be applicable to furthering our understanding of human cancer occurrence and the identification of novel tumour suppressors of therapeutic relevance.

It is an unfortunate fact that, due to their tractability as lab based models, the vast majority of species used as experimental models for human cancer, such as rodents and zebrafish, are short-lived. The evolutionary distance of the tumour suppressor machinery of these species from those of longer-lived species is probably a leading contributor to the recognised disparity between the effectiveness of pre-clinical treatments in these species and their diminished translational effectiveness in humans. Therefore, the study of cancer in wild populations of long-lived species using precision medicine approaches is likely to provide novel insight into evolutionarily conserved oncogenic and tumour suppressor functions and holds great promise for identifying more effective anti-cancer treatments with improved translational potential from animals to humans. Dittmer *et al*. (2015) highlight the importance of using multiple animal models to fully understand the biology of oncogenic herpesviruses. Not only can multiple animal models offer greater understanding of oncological causes and treatments, but closer examination and treatment of wildlife cancer epidemics using precision medicine approaches can provide lessons into the mechanisms of cancer development and indicate potential treatments for humans as well as wildlife. Thus,

human oncology can inform conservation efforts, and these efforts will in turn provide a deeper understanding of human cancer development and indicate more effective methods of treatment.

Zoonoses and anthroponoses

Exposure to domestic animal sources of infection and human-assisted exposure to wild sources have been identified as the two main drivers of disease emergence across host taxa (Tompkins *et al.*, 2015). The transmission of human infections to wildlife is becoming an increasing threat to vulnerable populations in the wild (Thompson, 2013). A broader understanding and enhanced databases related to emerging wildlife diseases will make us better positioned and prepared for future zoonotic (disease that can be transmitted to humans from animals) and anthroponotic (disease that can be transmitted to animals from humans) events. It has been found that the hosts of zoonotic emerging and re-emerging diseases are predominantly synanthropic (ecologically associated with humans) species, and these species are generally of low conservation concern (McFarlane *et al.*, 2012). This highlights the importance of applying cutting-edge techniques not only to endangered species but more widely across veterinary medicine, so that key disease transmission events may be identified and anticipated. The occurrences of zoonotic events, where animal pathogens evolve to become transmissible to humans, are likely to increase in line with the increased emergence of wildlife diseases, and outbreaks of diseases such as Ebola, SARS and the H5N1 virus have been devastating. It is imperative that such diseases are better understood in their natural hosts (Bean *et al.*, 2013). An increased understanding of wildlife diseases before they are transmitted to humans is likely to improve the response rate and development of human treatments, or may indeed prevent transmission to humans at all.

With the advent of genomic technology and computational analysis it may even become possible, once sufficient examples have been recorded, to predict in advance which disease strains are likely to cross the species barrier, for example by determining which specific genomic mutations allow viruses to be transmitted from animals to humans. Such predictions would require the accumulation of the genomes of a large collection of species-specific and cross-species disease variants, which would be accelerated by the wider adoption of precision wildlife medicine and genomic wildlife disease surveillance. Prediction capabilities would facilitate preventative actions, such as treating infected animals, and heighten our preparedness for those diseases which do spread to humans.

Anthroponotic events contribute further to the already serious, often human-induced, plight of endangered species. Stringent measures are now taken by primate researchers and ecotourists to avoid transmitting diseases from humans to great apes, including tuberculosis which is a major threat to great ape populations in equatorial Africa (Wolf *et al.*, 2014). Meanwhile, chytridiomycosis (see Wildlife Case Study 5) is believed to have been spread between endangered amphibians via human transport (Smith *et al.*, 2009).

Research into transmission of disease from wildlife to livestock, including zoonoses, is limited to a relatively small number of species (Wiethoelter *et al.*, 2015). Given the scale of the impact that such diseases can have (billions of dollars and hundreds or thousands of lives), it would be beneficial to society as well as wildlife to identify wildlife diseases and develop targeted treatments for them before they spread to livestock and humans (Zinsstag *et al.*, 2007).

Roadblocks to the implementation of precision wildlife medicine

While any novel but worthwhile endeavour naturally encounters roadblocks, precision wildlife medicine is in the favourable position that it can learn directly from recent efforts to encourage human medicine researchers, clinicians and patients to adopt precision medicine. Human medicine is providing a test bed to a vast array of novel approaches (technologies and analysis methodologies), and only those approaches which have been proven successful in the human setting need be adopted for wildlife medicine. A key objective of human precision medicine has been the integration of researchers, clinicians and patient groups through interdisciplinary education (CASyM Consortium, 2014). Likewise, precision wildlife medicine needs to overcome a knowledge gap by training wildlife-orientated researchers in the use of these approaches, and to encourage researchers already familiar with them (usually involved in human-orientated biomedical research) of the need and benefits of applying them to wildlife diseases. Similarly, educational activities are an effective means of convincing front line conservationists and veterinarians of the merit of investing time, energy and support to such precision wildlife medicine endeavours. This is especially important given that improvement to patient care/species conservation will not usually be achieved in the short-term.

Another roadblock to the implementation of precision wildlife medicine is the sheer variation of life histories in the animal kingdom which makes some species more amenable to these approaches than others (e.g. ease of monitoring and sampling). Though this is already a reality of all conservation biology, practices and infrastructure (zoos, rehab facilities, specialised wildlife organisations, etc.) are already in place for many endangered keystone species, which will facilitate obtaining the necessary access, samples and background ecological data for conducting precision wildlife studies.

Similarly, variation in species physiology could be problematic. While fundamental molecular and physiological functions are often evolutionarily conserved, it will be crucial to be cognisant of species differences. Such issues would be best overcome by the inclusion of veterinarians as key members of precision wildlife medicine studies, since they are well versed in considering the impact of species differences on treatment decisions and clinical responsiveness.

It is also possible that, for some diseases, precision medicine approaches would be cost prohibitive. This will largely depend on the relative worth placed on that species' survival. However, while precision approaches have high upfront costs, they are often ultimately more cost effective than traditional methods, especially when the price per data point and the cost of providing ineffective therapies are considered. Omic technologies also provide labour savings and time efficiencies over traditional molecular approaches. Furthermore, it is common practice to outsource key steps to service providers (e.g. sequencing companies) to avoid equipment and personnel costs, which will enable even wildlife disease researchers of modest means to have access to the latest technologies. Additionally, precision approaches tend to lead to more cost-effective treatments by only providing effective drugs to patients and by reducing the time an animal needs to spend in rehabilitation.

Finally, as recognised by human precision medicine advocates (CASyM Consortium, 2014), the most effective means of convincing all stakeholders of the merits of this precision approach over traditional approaches and their ability to overcome any roadblocks will be to provide concrete examples of the successful implementation of precision wildlife medicine, like some of the case studies described above.

Using precision wildlife medicine to unify human and animal health

The adoption of precision medicine approaches in conservation medicine is well aligned with the principles of the ongoing One Health and EcoHealth initiatives. EcoHealth 'strives for sustainable health of people, animals, and ecosystems by promoting discovery and understanding through transdisciplinary action-research' and One Health 'recognises that the health of humans, animals, and ecosystems is intimately connected and involves a coordinated, collaborative, interdisciplinary, and cross-sectoral approach to addressing a wide range of risks at the animal-human-ecosystem interface' (Zinsstag, 2012). The combination of the fields of human and veterinary medicine and ecology can only be of mutual benefit and will contribute to the advancement of each field. Many of the particularly detrimental wildlife diseases are a symptom of a stressed biome rather than being causative in themselves (as in the case of FP in sea turtles and cancer in beluga whales, see Wildlife Case Studies 1 and 2), so improved environmental health also has an important role in enhancing both animal and human health. A One Health/Ecohealth-informed approach to precision wildlife medicine can help to determine where attention should be focused, and improved surveillance and mobile technologies have the potential to dramatically improve outcomes of disease epidemics and zoonotic transmissions by allowing earlier identification of the type and transmission methods of diseases, and faster and efficient identification of affordable treatment options (Jenkins *et al.*, 2015, Karimuribo *et al.*, 2012).

We have outlined here how the more widespread adoption of precision medicine approaches to animal health and wildlife disease would dramatically enhance our capability to diagnose, monitor and treat emerging diseases detrimental to the conservation of endangered species. Integration of modern medical techniques with traditional vital conservation and environmental protection efforts will be essential to combat species decline. The general applicability of these omic approaches means that they are well suited to the investigation of

emerging wildlife diseases. Even in resource-limited conservation settings, these technologies mean that discoveries that previously would have required enormous collaborative effort and resources can now be made by smaller dedicated teams. The range of new emerging diseases means that more labour-intensive traditional approaches are no longer sufficient and that the rapid adoption of precision wildlife medicine (and its associated personnel, cost and time efficiencies) is required to meet current conservation needs. Meanwhile, the generation of omic-scale data of disease in wild species can broaden our basic understanding of disease mechanisms, thus improving how we tackle human health issues. Greater understanding of wildlife diseases combined with the associated knowledge-base enhancement through the inclusion of data from non-model species will greatly improve our ability to reliably translate lab-animal-based investigations to human medicine.

In summary, we believe that precision medicine has the potential to greatly improve outcomes for both wildlife and human diseases, and it is timely and imperative for precision medicine approaches to be applied to wildlife health.

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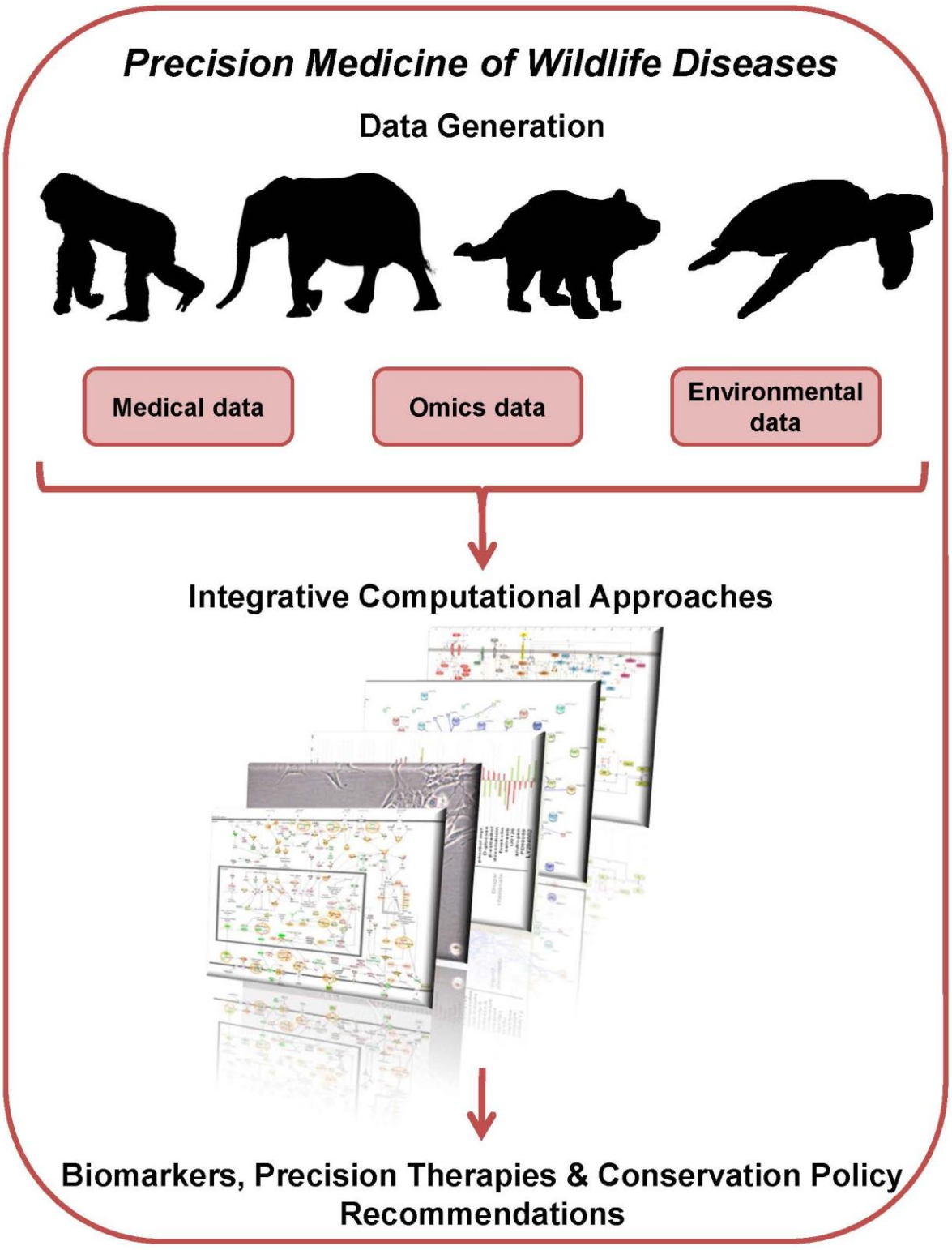
Figure Legends

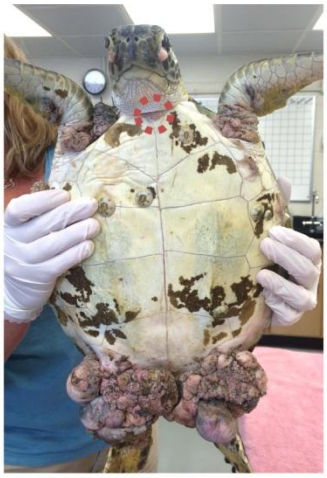
Figure 1. Schematic overview of the precision medicine approach to the study of wildlife disease. Images of animal silhouettes were obtained from the Phylopic database (http://phylopic.org/).

Figure 2. Fibropapilloma tumours in green sea turtles (*Chelonia mydas*). (A) Green turtle afflicted with neck and fin fibropapilloma tumours. **(B)** Green turtle severely afflicted with fibropapilloma tumours. Ventral neck tumour highlighted with a red dotted circled is the tumour which was imaged in panel C below. Image credits: Catherine Eastman. **(C)** Polyp-like papillary projections of a cutaneous fibropapilloma tumour from a green sea turtle, imaged under high magnification.



(a)

(b)



(c)