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Perspective

The Expectations and Challenges of Wildlife Disease Research in the Era of Genomics: Forecasting with a Horizon Scan-like Exercise

Robert R. Fitak, Jennifer D. Antonides, Eric J. Baitchman, Elisa Bonaccorso, Josephine Braun, Steven Kubiski, Elliott Chiu, Anna C. Fagre, Roderick B. Gagne, Justin S. Lee, Jennifer L. Malmberg, Mark D. Stenglein, Robert J. Dusek, David Forgacs, Nicholas M. Fountain-Jones, Marie L. J. Gilbertson, Katherine E. L. Worsley-Tonks, W. Chris Funk, Daryl R. Trumbo, Bruno M. Ghersi, Wray Grimaldi, Sara E. Heisel, Claire M. Jardine, Pauline L. Kamath, Dibesh Karmacharya, Christopher P. Kozakiewicz, Simona Kraberger, Dagan A. Loisel, Cait McDonald, Steven Miller, Devon O'Rourke, Caitlin N. Ott-Conn, Mónica Páez-Vacas, Alison J. Peel, Wendy C. Turner, Meredith C. VanAcker, Sue VandeWoude, and Jill Pecon-Slattery

From the Department of Biology, Duke University, Durham, NC, USA (Fitak); the Department of Forestry & Natural Resources, Purdue University, West Lafayette, IN (Antonides); the Zoo New England Division of Animal Health and Conservation, Boston, MA (Baitchman); the Instituto BIOSFERA and Colegio de Ciencias Biológicas y Ambientales, Universidad San Francisco de Quito, vía Interoceánica y Diego de Robles, Quito, Ecuador (Bonaccorso); the Institute for Conservation Research, San Diego Zoo Global, Escondido, CA (Braun and Kubiski); the Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO (Chiu, Fagre, Gagne, Lee, Malmberg, and Stenglein); the U. S. Geological Survey, National Wildlife Health Center, Madison, WI (Dusek); the Interdisciplinary Graduate Program of Genetics, Texas A&M University, College Station, TX (Forgacs); the Department of Veterinary Population Medicine, University of Minnesota, St. Paul, MN (Fountain-Jones, Gilbertson, and Worsley-Tonks); the Department of Biology, Colorado State University, Fort Collins, CO (Funk and Trumbo); the University of Tennessee, Knoxville, TN (Ghersi); the Encinitas, CA (Grimaldi); the Odum School of Ecology, University of Georgia, Athens, GA (Heisel); the Department of Pathobiology, Canadian Wildlife Health Cooperative, University of Guelph, Guelph, Ontario, Canada (Jardine); the School of Food and Agriculture, University of Maine, Orono, ME (Kamath); the Center for Molecular Dynamics Nepal, Kathmandu, Nepal (Karmacharya); the School of Biological Sciences, University of Tasmania, Hobart, Tasmania, Australia (Kozakiewicz); the The Biodesign Center for Fundamental and Applied Microbiomics, Center for Evolution and Medicine, School of Life Sciences, Arizona State University, Tempe, AZ (Kraberger); the Department of Biology, Saint Michael's College, Colchester, VT (Loisel); the Department of Ecology & Evolutionary Biology, Cornell University, Ithaca, NY (McDonald); the Department of Biology, Drexel University, Philadelphia, PA (Miller); the University of New Hampshire, Durham NH (O'Rourke); the Michigan Department of Natural Resources, Wildlife Disease Laboratory, Lansing, MI (Ott-Conn); the Centro de Investigación de la Biodiversidad y Cambio Climático (BioCamb), Facultad de Ciencias de Medio Ambiente, Universidad Tecnológica Indoamérica, Machala y Sabanilla, Quito, Ecuador (Páez-Vacas); the Environmental Futures Research Institute, Griffith University, Nathan, Queensland, Australia (Peel); the Department of Biological Sciences, University at Albany, State University of New York, Albany, NY (Turner); the Department of Ecology, Evolution, and

Environmental Biology, Columbia University, New York, NY (VanAcker); the College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO (VandeWoude); and the Center for Species Survival, Smithsonian Conservation Biology Institute-National Zoological Park, Front Royal, VA (Pecon-Slattery).

Address correspondence to R. R. Fitak at the address above, or e-mail: rfitak9@gmail.com.

Address also correspondence to J. Pecon-Slattery at the address above, or e-mail: slatteryjp@si.edu.

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Corresponding Editor: Robert C. Fleischer

Abstract

The outbreak and transmission of disease-causing pathogens are contributing to the unprecedented rate of biodiversity decline. Recent advances in genomics have coalesced into powerful tools to monitor, detect, and reconstruct the role of pathogens impacting wildlife populations. Wildlife researchers are thus uniquely positioned to merge ecological and evolutionary studies with genomic technologies to exploit unprecedented "Big Data" tools in disease research; however, many researchers lack the training and expertise required to use these computationally intensive methodologies. To address this disparity, the inaugural "Genomics of Disease in Wildlife" workshop assembled early to mid-career professionals with expertise across scientific disciplines (e.g., genomics, wildlife biology, veterinary sciences, and conservation management) for training in the application of genomic tools to wildlife disease research. A horizon scanning-like exercise, an activity to identify forthcoming trends and challenges, performed by the workshop participants identified and discussed 5 themes considered to be the most pressing to the application of genomics in wildlife disease research: 1) "Improving communication," 2) "Methodological and analytical advancements," 3) "Translation into practice," 4) "Integrating landscape ecology and genomics," and 5) "Emerging new questions." Wide-ranging solutions from the horizon scan were international in scope, itemized both deficiencies and strengths in wildlife genomic initiatives, promoted the use of genomic technologies to unite wildlife and human disease research, and advocated best practices for optimal use of genomic tools in wildlife disease projects. The results offer a glimpse of the potential revolution in human and wildlife disease research possible through multi-disciplinary collaborations at local, regional, and global scales.

Keywords: biodiversity, bioinformatics, comparative genomics, host, next generation DNA sequencing, pathogen

Advances in genomic methodologies are rapidly transforming research in infectious diseases. These techniques are improving the surveillance and management of disease outbreaks (Gilmour et al. 2013; Gire et al. 2014), identifying novel targets for vaccines and other treatments (Doolan et al. 2014), and enhancing the understanding of evolutionary relationships between hosts and pathogens (Rausell and Telenti 2014). Although genomics has become a mainstay in public health research—especially in diseases affecting humans and livestock—it remains relatively underutilized in wildlife disease research. Recent epidemics of chytridiomycosis in amphibians and white-nose syndrome in bats, for example, have decimated host populations, highlighting the need for improved detection and response (Fisher et al. 2012; Grogan et al. 2014). Although these cases and others are beginning to actively utilize genomics, many wildlife disease researchers and conservation programs could still benefit from increased application of genomic technologies (reviewed in Blanchong et al. 2016). In addition to biodiversity conservation and management, the implications of improved wildlife disease research, such as preventing spillover of emerging zoonoses (Plowright et al. 2016), also have critical ramifications in human health. More than 60% of emerging infectious diseases are zoonotic, and 72% of these zoonoses originate in wildlife (Jones et al. 2008). This underscores the importance of approaches such as the One Health paradigm, which aim to mitigate the consequences of emerging infectious diseases through holistic, interdisciplinary, and collaborative efforts (Cunningham et al. 2017).

The current era of genomics and big data has simultaneously included the development of computational tools necessary to process these data. Unfortunately, these tools require specific training and skill sets often lacking in "wet lab" and field researchers who are instead dependent on the support of bioinformaticians and statisticians (Carvalho and Rustici 2013). This apparent gap between the generation of genomic data by researchers and the analysis has become a crucial bottleneck in the translation of results into application and management (Green and Guyer 2011; Carvalho and Rustici 2013). This gap will continue to expand with the rapid decline in costs and increased availability of next-generation sequencing (NGS) technologies. As a result, wildlife disease researchers must improve their bioinformatic and computational skills to harness the power of the genomic tools available. Even if collaborating with bioinformaticians, wildlife researchers could benefit from an improved understanding of the principles and methods of genomic analyses.

To provide wildlife disease researchers with initial training and familiarity with bioinformatic tools, a workshop, "Genomics

of Disease in Wildlife 2017" (GDW2017; https://gdwworkshop.colostate.edu/), was held at Colorado State University in Fort Collins, CO in June 2017. This workshop brought together wildlife biologists, veterinarians, wildlife managers, and genome scientists from around the world seeking to incorporate genomics into their wildlife disease research programs. The GDW2017 workshop included intensive, hands-on computational training in genome assembly, read mapping, whole-genome alignment, phylogenomics, detecting selection, population genomics, and variant identification. In addition to training, distinguished researchers in the field of wildlife disease gave short talks and plenary lectures.

As a part of GDW2017 we used a horizon scanning-like exercise (see *Methods* section) to outline the most significant questions and challenges facing the field and to identify the best approaches to manage and/or prepare for them in the near future. Horizon scanning is a method that systematically identifies "incipient trends, opportunities and risks that may affect the probability of achieving management goals and objectives" (Sutherland et al. 2010). Additionally, horizon scanning emphasizes new technology while exploring unexpected issues pushing the boundary of current thinking. Commonly employed by corporations and governmental institutions, horizon scans are becoming increasingly popular among scientists. For example, horizon scans have been performed annually since 2010 to assess global concerns for biodiversity conservation (Sutherland et al. 2010, 2017), to predict challenges in farm animal genomic resource management (Bruford et al. 2015), and to evaluate threats from invasive species (Roy et al. 2014). Here, we describe the results from our horizon scanning approach at GDW2017 that investigated the issues and challenges facing the use of genomics in wildlife disease research. We emphasize that the results discussed below are not meant to be an exhaustive review of the subject, but rather to introduce readers, especially those without genomics expertise, to the most recent techniques, applications, and emerging difficulties. We chose these particular topics because they represented a majority of the discussion among our diverse panel of participants. However, the omission of a particular topic as it relates to genomic studies of wildlife disease does not imply a lack of importance, but rather the limitations of time for the exercise, breadth of participant backgrounds, scope of our findings, and the particular snapshot in time taken for such a rapidly changing field.

Methods

We used a horizon scanning-like approach comparable with that employed by Bruford et al. (2015). Rather than strict adherence to horizon scanning methods such as the Delphi technique (Mukherjee et al. 2015), this informal approach retained some attributes to minimize potential biases or effects from social pressures, such as an anonymous submission process, while maintaining a face-to-face discussion component. At the beginning of the workshop, participants were asked to anonymously submit up to 5 questions or challenges that they felt were of utmost importance to the field of wildlife disease genomics. Participants were given a total of 5 days during the workshop to prepare their submissions. After all submissions were collected, they were organized into categories based upon similar themes or topics represented. A moderator was assigned to each category, and the workshop participants self-divided among them. The moderator and group participants then held a 2-h discussion of the topics in their category and summarized their findings with detailed notes. Afterwards, all groups reconvened to share their findings with the remaining participants and for a consensus discussion lasting approximately 30 min. Ideally, additional iterations of survey and discussion would have been performed to maximize the benefits of the Delphi technique to reach a consensus and resolve potential conflicts among participants (Mukherjee et al. 2015), but time restrictions did not permit this. As a result, the findings presented below are limited to discussion that took place during the workshop and thus reflect the ideas, views, experiences, and potential biases of this specific panel of participants.

Results and Discussion

A total of 38 people (20 women and 18 men) participated in the exercise. This included the 24 workshop trainees representing 6 countries (Australia, Canada, Ecuador, New Zealand, Nepal, and the United States). Among them were 11 faculty and other wildlife professionals, 2 postdoctoral scholars, and 11 PhD or DVM/PhD students. The remaining participants included 7 instructors, whose backgrounds encompassed a multitude of applications of genomics and bioinformatics to questions in wildlife host and pathogen research, and an additional 7 auditors (senior graduate students and post-docs).

Over the 5-day period, 48 contributions were received (Table 1). The most common questions were often associated with improved training or communication between disease biologists and bioinformaticians (5/48 contributions) and for standardization of genomic methods and/or quality assessment (5/48 contributions). The contributions were subsequently divided into 5 categories, or themes, although considerable overlap often existed among them (Figure 1). These 5 themes included 1) "Improving communication," 2) "Methodological and analytical advancements," 3) "Translation into practice," 4) "Integrating landscape ecology and genomics," and 5) "Emerging new questions." The findings and discussions of each group are summarized below.

Improving Communication

The discourse among this group's participants offered an international perspective, including discussions on experience in the study of wildlife disease in North America, South America, Asia, Africa, Australia, and Antarctica. This session centered on the value of communication when fostering partnerships, collecting samples and data, and sharing resources—with the ultimate goal being collaboration between genome scientists and local researchers and governments faced with the reality of disease outbreaks in remote locations or developing countries.

New Partnerships

The emergence and reemergence of zoonotic disease continually threatens global health and offers remarkable opportunities to create new international partnerships for effectively controlling and ameliorating future outbreaks or preventing unnecessary mitigation efforts such as culling of wildlife populations (Olival 2016). Efforts to better predict outbreaks and disease risk motivate current studies on environmental factors, wildlife biodiversity, and emerging zoonotic disease on a global scale and support unified international intervention (Ostfeld 2009; Han et al. 2016; Allen et al. 2017). For example, the changes implemented between the coronavirus (CoV) outbreak of SARS in 2003 compared with the related MERS outbreak in Saudi Arabia in 2014 indicated improved communications in rapid response to zoonotic disease by public health officials in

Table 1.

List of the responses received from the horizon scan's participants organized into 5 themes

Category	Questions submitted
Improving communication	• How do we improve the communication between biologists and bioinformaticians? • How do we improve the communication across disciplines to ensure everyone is "speaking the same language"? • How can we enhance communication/understanding to bridge the gap between the computer scientists/algorithm experts and the biological scientist studying wildlife disease? • Can we improve the training? Or better yet, initiate training in genomics? • In developing countries, wildlife disease researchers had recently caught up with the genetic techniques, but now with genomics have again fallen behind due to a lack of training and financial resources. What are the strategies to mitigate this situation? • How do we improve training in genomics in developing countries? • How do we improve access to data and foster new collaborations? • How can we identify more funding opportunities? • Can web or other portals be established to link people with research, training, and funding opportunities? • What are the stable sources of funding that can traverse a dynamic and fluctuating political atmosphere? • What funding opportunities are available to support research, training, and resource development for GDW projects? • What publication options are most impactful for studies of GDW? That is, what specialty journals are most relevant for publications in this realm?
Methodological and analytical advancements	• What are the best approaches to optimize obtaining genomic data, both host and pathogen, from non-invasive sampling? • How do we maximize or improve the collection of genomic data (host and pathogen) from non-invasive sampling techniques? • How do we standardize methods for better comparisons across studies? • Will machine learning approaches be a valuable statistical tool to integrate massive datasets of genomes (host and pathogen), environmental data, pathogen data, medicine, etc? • Can methods to detect selection on highly recombining sequences (e.g., viruses) be improved? • What advantages will single-molecule sequencing provide for GDW research? • How much can you trust sequence quality of publicly available genetic data? • How do we link genomic data between the host and pathogen? • What is the optimal strategy to balance the relationship between the number of samples vs the amount of sequence data? • What are the best methods of sampling in order to find potential selection occurring between hosts and pathogens? • How does one balance cost and coverage of the genome to find host adaptation of the disease? • Can whole genome studies be reduced to a core "step-by-step" framework applicable to a majority and provide consistency and comparison across studies? • Can a standardized or core set of requirements be developed to assess the quality of published genomes/exomes? • What are resources for analyzing data from raw files to figure form without a bioinformatician? • Where should the technical focus of GDW research lie when it comes to sequence data? Should DNA extraction and library prep be left to commercial services in order to direct attention to the biological aspects of GDW? • Will the field of GDW benefit from many small core sequencing facilities or several large core centers that are cheaper?
Translation into practice	• What are approaches for determining what agents identified by metagenomics analysis are actually pathogenic? • What is the interaction between pathogens/potential pathogens and host microbiome? • What can we learn about coinfections/microbial interactions that lead to homeostasis or disease? • How do we handle co-infection data? • How do we foster continued research on the candidate genes or regions reported from the genomics studies? • How do we translate the findings from genomics directly into conservation, medical, and/or disease research? • How do we bridge the gap between the results of genomic studies and the application in the management of wildlife and their associated diseases?
Integrating landscape ecology and genomics	• How do we understand pathogen transmission between wildlife? • How do we better integrate databases of genomic/genetic data, landscape/ecological data, disease/pathogen data, and epidemiological surveys? • How do we integrate phylogenetic/phylodynamic data and landscape ecology to inform cross-species transmission in a changing landscape? • How do anthropogenic influences (urbanization, extraction, road building, transport/movement of animals, etc.) alter the landscape of wildlife diseases? • With increased urban greening initiatives and the return of wildlife to urban landscapes, how can we manage habitat for wildlife health and prevent infectious disease outbreaks? • How do we link conservation genetics and landscape ecology through spatial analysis? • How does wildlife microbiome vary by species and environment? Since wildlife are species least likely to encounter pharmaceuticals that artificially alter microbial populations, could studies of wildlife microbiome reflect natural microbiome/host interactions?
Emerging new questions	• In human medicine finding genes associated with increased disease risk has been difficult. Because natural selection and evolutionary arms races can proceed more naturally in wildlife than human populations (due to modern medicine) would we expect to more readily find alleles associated with disease—can this inform these efforts in human medicine? • What are host mechanisms for disease resistance? How does host immune response drive pathogen evolution and vice versa? • How do we leverage genomics to understand phenotypic plasticity and its relationship to host/pathogen disease dynamics? • How do we link phylogenetic data to network modeling? • How do we apply phylogenomic and phylodynamic data to slowly evolving pathogens? • How can you recreate accurate phylogenies for rapidly evolving pathogens, such as viruses, that can determine deep evolutionary lineages?

GDW, genomics of disease in wildlife.

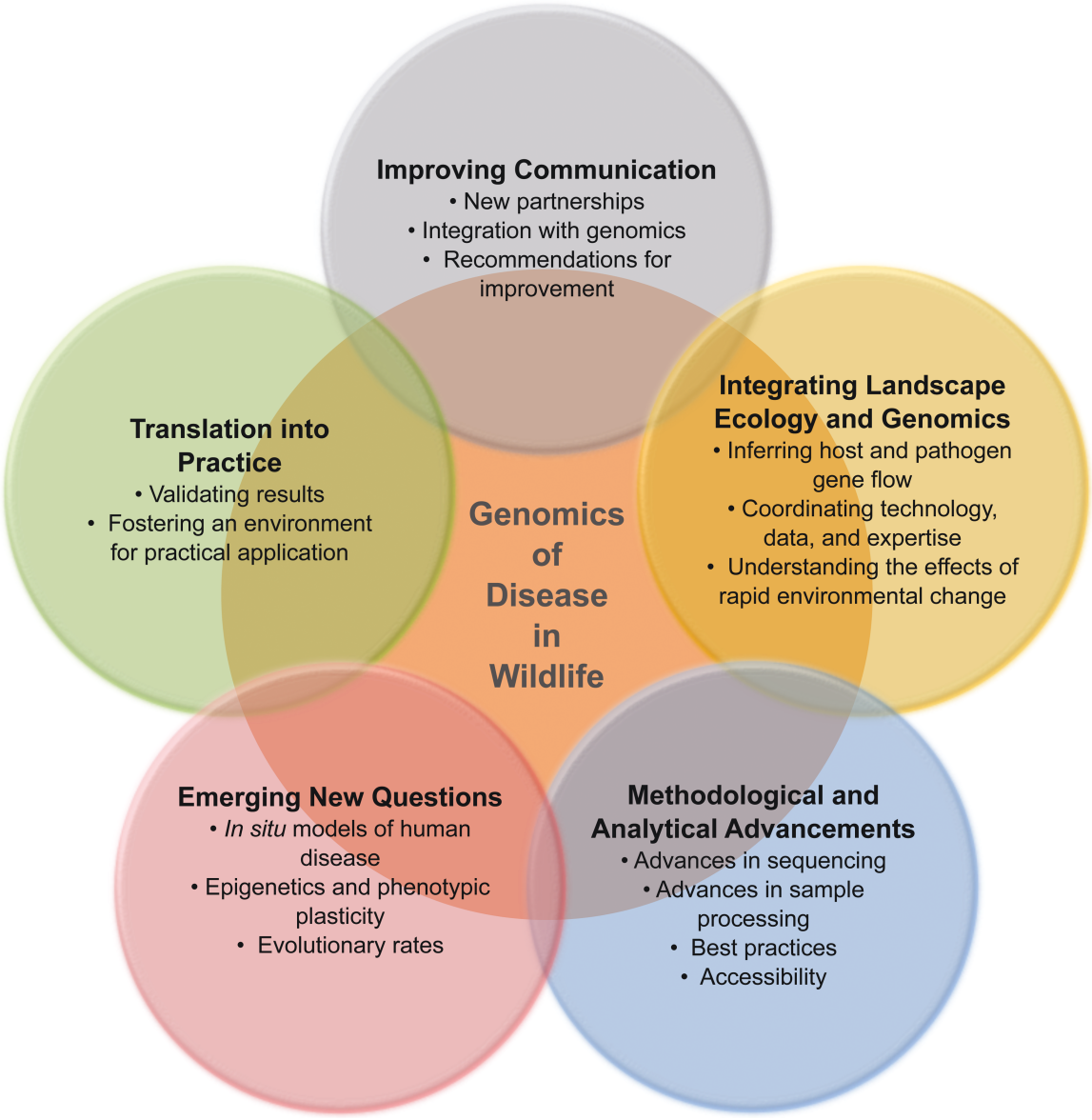

Figure 1. Summary of the discussion among workshop participants within each of the 5 themes. Although each theme in some way intersected with each of the others, overlapping circles indicate extensive overlap in discussion between themes.

both the affected area and the global community (Kuehn 2013). Major ongoing initiatives to prevent pandemics, such as new global surveillance networks, health care infrastructure improvements, and partnerships with the World Health Organization, were triggered by the lessons learned from the SARS-CoV epidemic (Marston et al. 2017), Ebola outbreaks, and others (Halliday et al. 2017). Such examples underscore the need for human clinicians, wildlife researchers, veterinarians, conservation managers, and genomic scientists to collaborate and promote multi-disciplinary approaches to global disease solutions.

The One Health Initiative is a progressive multi-discipline program that recognizes the intricate interplay among human health and behavior, wildlife disease, and environmental parameters (Cleaveland et al. 2017; Cunningham et al. 2017; Kelly et al. 2017). One of the invited plenary speakers for GDW2017, Dr Christine Krueder Johnson, a Professor at the University of California-Davis, provided a first-hand account of the PREDICT surveillance program. Funded by the United States Agency for International Development (USAID), PREDICT formed partnerships with research institutions within the USA (Smithsonian Institution, UC-Davis, EcoHealth Alliance, Metabiota, Inc., and the Wildlife Conservation Society) and local officials in over 20 developing countries. These partnerships led to large-scale surveillance of animals harboring potential zoonotic species and/or actively shedding viruses by screening thousands of samples from human habitation and marketplaces in South America, Asia, and Africa.

Integration with Genomics

Wildlife biologists are examining disease emergence and transmission in natural populations, whose interface with human urbanization or agricultural practices can cause drastic effects on species survival and/or increase the frequency of interspecies transmission

of pathogens. In North America, genetic studies of puma (*Puma concolor*) and bobcat (*Lynx rufus*) populations indicate altered patterns of viral disease transmission and animal health in response to anthropogenic changes (Lee et al. 2012; Ernest et al. 2014; Carver et al. 2016; Fountain-Jones et al. 2017). Moreover, projects that integrate NGS tools can provide detailed information on the transmission of transcontinental diseases such as the spread of rabies in North America and in East Africa (Brunker et al. 2015; Trewby et al. 2017), and diseases circulating between wild and domesticated livestock on local and global scales (Nomikou et al. 2015; Kamath et al. 2016; Trewby et al. 2016; Dippenaar et al. 2017; Grear et al. 2018).

The group concurred that integration of comparative genomic tools using NGS data are uniquely able to unite public health research with that of wildlife disease. These tools are essential to identify factors, such as genome structure, content and organization, the geographic origin of zoonotic outbreaks, identification of the emergent strain, rates of transmission, regional and global patterns of transmission and dissemination, virulence factors, and potential targets for drug and vaccine research. Further, host genomic studies in adaptive evolution and speciation, population structure and dynamics, patterns of diversity present within host genes linked with fitness and disease susceptibility, and levels of inbreeding and reproductive fitness regulating species survival are crucial factors in predicting the potential effects of an emergent pathogen (McKnight et al. 2017).

Recommendations to Improve Communication

Recommendations made by the group centered on communication mechanisms to rapidly connect advances in genomic tools and equipment with regional researchers and agencies directly managing disease outbreaks in wildlife populations. The resulting partnerships would pave the way for eliciting local community interest and involvement, a vital step in developing policy to benefit both wildlife survival and human health. One suggestion was to coordinate efforts with existing programs such as One Health surveillance, NGOs, and government agencies to establish local or regional partnerships for NGS applications to host and pathogen. This direct association could enable rapid field-based identification of pathogen strains during disease outbreaks as illustrated by the recent Ebola outbreak in Africa (Arias et al. 2016; Quick et al. 2016; Dudas et al. 2017).

A second recommendation was to take advantage of the latest advances in sample and data sharing so that all partners of a project are equally informed in "real time." Local wildlife field biologists play a vital role in epidemiological investigations, collecting crucial samples for genomic characterization and medical review. Subsequent research in laboratory settings can often take years, with few updates between genomic scientists and field researchers. This workshop group proposed that once established, partnerships implement regular meetings and workshops among all participants and take advantage of additional communications facilitated by online tools of webcasts, video conferences, workshops, and secure repositories for sharing data and results.

Third, the workshop participants recommended that innovative outreach and training programs be created through these dynamic international partnerships. For example, the North Pacific Research Board (http://www.nprb.org) includes funding for education and outreach initiatives in all research awards. Increased communication between laboratory and field science could also generate new approaches based on multidisciplinary expertise that will not only benefit animal health and survival but develop innovative methods to involve and educate local communities. The group's participants proposed education tools within schools that used community participation in projects focused on the ecology, health, and conservation of iconic wildlife species of the region.

Successful implementation of these programs in developing countries, which can be hampered by insufficient funds for wildlife genomics, will require better ways to connect necessary resources with key wildlife, conservation, and biomedical personnel conducting research within those countries. The group suggested a process that includes 1) unifying disparate wildlife and biomedical organizations and key personnel conducting research within developing countries through shared objectives in reducing the outbreaks of disease, 2) connecting resources for funding such organizations through new collaborations such as PREDICT and One Health initiatives seeking samples of host and pathogen for genomic analyses, 3) providing sponsorships and scholarships to support hands-on training for personnel in developing countries in genomic technologies and bioinformatic methods, and 4) inviting stakeholders and key opinion leaders, biomedical and scientific funding agencies, NGOs, and biotechnology companies interested in expanding the role of genomic technologies to serve as sponsors for researchers from developing countries (see Funding section). The GDW2017 workshop illustrated the success of connecting generous and crucial sponsors from diverse organizations to fund scholarships and hands-on training of key participants from developing countries and creating a new network of world-wide colleagues to address emerging diseases with genomic tools.

Finally, it was recommended that wildlife disease researchers be encouraged to publish in open access peer-reviewed journals or otherwise make their results and publications as accessible as possible (e.g., using social media platforms) to allow developing world scientists and government leaders to keep current with the latest advances in genomic tools and technology. Sharing the latest information on strategies to ameliorate wildlife disease outbreaks could benefit local educators and administrators within affected communities.

Methodological and Analytical Advancements

Genomics is a rapidly evolving field, and this workshop group considered the methodological and technical advances that are likely to impact wildlife disease research. A variety of anticipated impacts were discussed, such as improvements to sample processing, library preparation, sequencing, and computational methodology. The potential benefits of increased standardization and adoption of best practices were considered in the context of future genomic studies performed in resource-limited settings and by scientists without formal bioinformatics training.

Advances in Sequencing

Genomics methodology and technology are developing at an astonishing speed. One of the primary drivers of this trend has been the introduction of new sequencing instruments (Heather and Chain 2016), typically categorized by read length output. Short read sequencers (e.g., Illumina In., San Diego, CA) are extensively used in wildlife research, particularly when a suitable reference genome exists, and produce millions of sequences (50–300 bp) with low error rates (~1%). By contrast, long read sequencing technologies, such as those produced by Pacific Biosciences (Menlo Park, CA) and Oxford Nanopore Technologies (Oxford, UK), can generate sequences >10 kb in length albeit at high error rates (up to ~25%;

Goodwin et al. 2016). Long sequence reads offer unique advantages in scaffolding de novo genome and transcriptome assemblies, as well as characterizing structural variation (Goodwin et al. 2015). For example, long read technologies have been applied to sequence, directly from a clinical sample, the complete genome of a fur seal parapoxvirus (Günther et al. 2017), a group of viruses known for large genomes up to 360 kb in length (Haller et al. 2014). Inexpensive and ultra-portable sequencers (e.g., the MinION from Oxford Nanopore Technologies) provide new capabilities for field research or resource-limited settings (Faria et al. 2016). As the next decade unfolds, innovations in sequencing technology are expected to continue along with declining costs and increased accessibility to a variety of researchers.

Advances in Sample Processing

Progress in methods used in sample collection and library preparation further expand the variety of tissue types, quantities, and genomic targets available for DNA sequencing. In particular, wildlife biologists are interested in collecting samples with as little disturbance to the organisms as possible—often referred to as "noninvasive" sampling. Not only do these methods minimize stress, but they may be the only option for highly elusive animals. Unfortunately, these samples, which can include feces, shed skin, hair, and teeth among others, regularly result in DNA that is difficult to sequence or that otherwise confounds many genomic analyses. These difficulties can be caused by DNA that is low in quantity, degraded, or that contains inhibitory compounds. DNA isolated from fecal material has been the most promising for wildlife disease research because not only is it non-invasive, but feces can also provide insight into the diet and parasite load (e.g., Schwab et al. 2011; Carver et al. 2012; Granroth-Wilding et al. 2017). Recently, new techniques to enrich for host DNA from feces has greatly improved sequence output and quality, and these types of improvements can facilitate future work from these samples (Perry et al. 2010; Hart et al. 2015; Mathay et al. 2015). Similarly, further development and validation of methods for collecting and sequencing nucleic acids from samples that require direct contact but are relatively easy to obtain, such as saliva, could also be beneficial (Lobo et al. 2015). Increasingly, clever uses of archival museum or fossilized specimens have generated usable DNA providing a window into host–pathogen interactions on timescales of hundreds to thousands of years (Avila-Arcos et al. 2013; Weyrich et al. 2017).

Additional innovations include the development of sequencing libraries with specific targets for genomic investigations. Targeted capture techniques, which utilize hybridization oligonucleotide probes to enrich for specific nucleic acids, have become popular for their array of uses in addition to their application in noninvasive or ancient sample specimens (Perry et al. 2010; Campana et al. 2016; Lee et al. 2017). The primary limitation of these techniques is that target sequences, from pathogens for example, must be known a priori, making the discovery of novel pathogens more difficult. A good example is the work by Lee et al. (2017), who designed capture probes for a variety of felid pathogens. This method enriched pathogen DNA from 58- to 56 million-fold over the host DNA, and identified 31 pathogens across 9 taxa, 11 of which were undetected using PCR. However, this method also failed to detect one virus target previously identified by nested PCR in 3 samples, suggesting future improvements in sensitivity are warranted. A second example is the "EctoBaits" targeted assay developed by Campana et al. (2016). This assay can simultaneously identify sequence targets for 266 vertebrate host species, 66 parasite species, 84 pathogen strains from the northeastern United States and East Africa. The authors demonstrated the utility and cost-effectiveness of the assay relative to traditional PCR-based screening. However, the assay can be susceptible to false positives, and as mentioned above, is limited primarily to known taxa. Yet, expansion of and improvements to assays such as EctoBaits could be critical to rapid characterization of future outbreaks whilst enabling cross-laboratory consistency.

Other library preparation methods include those primarily for host population genetics, such as pooled sequencing (pool-seq), which samples a mixture of individuals and is particularly useful for assessing allele frequencies in populations (Schlötterer et al. 2014). Methods including duplex sequencing (duplex-seq) and circular sequencing (cirseq) have been developed to specifically detect ultra-rare variants in populations of viruses and distinguish these variants from sequencing errors (Acevedo and Andino 2014; Kennedy et al. 2014). From a functional perspective, techniques like STARR-seq (Arnold et al. 2013) and mSTARR-seq (Lea et al. 2018) provide unprecedented evidence for the role of enhancers or methylated regions, respectively, on gene expression. The techniques mentioned here are only a small subset of the numerous creative methods by which sequencing libraries can be prepared to target nucleic acids under specific circumstances. Further development of these approaches, especially in the context of pathogens and new, long-read sequencing technologies, will be invaluable for the genomic studies of wildlife diseases.

Best Practices

Another important consideration related to rapid methodological advancements is the concept of "best practices" or "minimum acceptable procedures." This issue applies to study design, sample collection, sequencing, analysis methodology, publication, and data and software sharing (Vaught et al. 2010; Whitlock 2011; Sandve et al. 2013; Olson et al. 2015; Conesa et al. 2016; Wilson et al. 2017). The motivations for adopting a set of standardized, or best, practices include 1) the ability to compare studies, 2) increased reproducibility, 3) efficiency gains from sharing raw data, methods, and computer code, and 4) easier adoption of genomics by inexperienced researchers. The discussants advocated that best practices be developed and formally adopted by the wildlife (disease) genomics community, recommending a future review article to initiate the discussion.

Accessibility

Another major challenge is that wildlife disease research may often be conducted in resource-limited settings and by individuals without formal training in bioinformatics (see *Improving Communication* section). Wildlife research is performed throughout the world, yet where suitable research infrastructure is unavailable, samples must be exported for processing and analysis. This presents additional legal, ethical, and administrative issues, especially for select agents and when researching endangered or otherwise protected animals (Renner et al. 2012). A related challenge is that wildlife researchers may lack the background in or access to genomics and computing necessary to take full advantage of the most powerful modern research techniques (Attwood et al. 2017), thus motivating the development of GDW2017. The discussants were split on whether wildlife researchers in these developing regions should pair with external sequencing facilities and bioinformaticians or whether they would be better served by doing the work internally. Those in favor of partnering with external experts noted that wildlife researchers

already need to have an extensive knowledge base and pointed to the efficiency gained from collaboration. Those in favor of researchers performing their own sequencing and analysis noted that collaborators may not necessarily understand the biology of the system being studied and might miss or overlook key pieces of a more complex puzzle. In any case, there was agreement that increased capacity building in the form of research infrastructure and training in genomics, particularly in resource-poor countries, could undoubtedly accelerate the progress of wildlife genomics.

Translation into Practice

One of the ultimate goals of genomics research in wildlife disease is to translate the findings into a tool, test, or intervention that can benefit the species of interest. In human medicine, the chasm between genomic discoveries and their clinical validity and utility has been of substantial concern, and programs such as the Genomic Applications in Practice and Prevention Network have been created to address this issue (Khoury et al. 2009). In the context of wildlife, the gap between genomics research and application is arguably much larger than in humans (Shafer et al. 2015). So how do researchers convert their findings into a meaningful, effective, and understandable implementation for wildlife managers and stakeholders? The discussion within this theme centered on 2 principles: 1) validating or expanding initial genomic findings through additional research, and 2) fostering an environment to promote translation into practice.

Validating Genomic Studies

A cornerstone of genomics and NGS in disease research is the rapid, high-throughput, and precise identification of pathogens. As genome sequencing can be vulnerable to certain errors and biases, linking candidate pathogens to disease can be a difficult task. There must also be considerable confidence in scientific accuracy in order to translate results into practice. As a result, follow-up studies are imperative to replicate findings and more clearly elucidate causality and establish links with disease (Chiu 2013). Many of these studies should attempt to address criteria such as Koch's postulates, which target pathogen isolation and culture, although other considerations, such as serologic or molecular criteria, may also be appropriate (e.g., Fredricks and Relman 1996; Lipkin 2010; Fedak et al. 2015). To meet these strict requirements, pathogenesis studies on tissues, combined with epidemiological evidence garnered from well-developed collections of metadata, are critical to establishing links between pathogen discovery and disease. These criteria, however, are not suited to polymicrobial infections (e.g., Meyer et al. 2017) and defining the constituents of a "normal" versus a "pathogen" metagenome in the context of the environmental, immunological, and transcriptomic factors. Finally, in addition to pathogen discovery, the same principles of replication and functional validation apply to all aspects of host and pathogen biology, for example when identifying resistance loci in a host or virulence genes in a pathogen using genomic association-based techniques (Kraft et al. 2009).

Fostering an Environment for Practical Applications

To properly translate genomic findings into practice, appropriate infrastructure, resources, and communication networks are required. One important resource is a "biobank" of healthy and pathological specimens (Vaught 2016). Although numerous biobanks already exist for genetic material, cell culture, gametes, and embryos from wild animals and plants (e.g., Frozen Zoo—http://institute.sandiegozoo.org/resources/frozen-zoo®; Frozen Ark—https://frozenark.org, Williams 2004), pathological specimens from diseased and also healthy wildlife are less common (although see González et al. 2017 for a good example in fish). These resources, along with sufficient metadata (Droege et al. 2016), are critical for the comparison of future samples with current specimens to evaluate pathogen prevalence and association with disease. Likewise, storage of various types of genomic data, such as sequence and expression data, in public databases (Duke and Porter 2013) could encourage and facilitate replication, follow-up studies, and development of results into application. Moreover, innovative techniques, such as gene set context analysis (Ji et al. 2016), integrate massive genomic datasets stored across public databases enabling new discoveries not previously possible from any single study.

Genomic studies of wildlife disease could ideally engage multidisciplinary communication networks among biologists, veterinarians, data and bioinformatic personnel, local communities, state agencies, law enforcement, and funding organizations. A popular approach is "mainstreaming biodiversity" (Redford et al. 2015): a collective set of processes designed to change practices in the public and private sector by demonstrating the importance of conserving biodiversity for achieving economic, policy, and development outcomes. Wildlife disease biologists can harness this approach to increase engagement of stakeholders by demonstrating the local benefits of applied wildlife disease monitoring and intervention. Finally, a robust framework for discovery, follow-up, and communication needs to be established for the field and we suggest integrating principles, analytical workflow, techniques, and bioinformatics established for human biomedical genomics (e.g., guidelines posited by the Broad Institute, https://software.broadinstitute.org/gatk/best-practices/) to develop similar approaches in wildlife species and their pathogens. Although a "gold standard" may not be appropriate across all situations, a solid template for how to approach, execute, and implement population health efforts will benefit all parties involved.

Integrating Landscape Ecology and Genomics

Landscape ecology generally addresses the contribution of spatial organization on large scales to ecological processes (Turner and Gardner 2015). The field of landscape genetics is an extension of landscape ecology that investigates the role of landscape ecology in shaping genetic variation (Manel et al. 2003). This field has expanded tremendously and now includes systems of wildlife hosts and pathogens (Clements and Pfeiffer 2009; Biek and Real 2010). More recently, the field has naturally shifted toward landscape genomics, transformed by advances in NGS, cutting-edge remote sensing, and GIS technologies (Kool et al. 2013). Taken together, the incorporation of landscape genomics into wildlife disease biology promises improved prediction of disease risk, transmission, and prevention (Schwabl et al. 2017). Three general prospects for the future of integrating landscape ecology with wildlife disease materialized from the horizon scan discussion: 1) inferring host and pathogen gene flow, 2) coordinating technology, data, and expertise, and 3) understanding the effects of rapid environmental change.

Inferring Host and Pathogen Gene Flow

Relative to host species, most pathogens evolve substantially faster and have markedly different life histories; including evolution both within and external to the host (Metcalf et al. 2015). An excellent method to assess differential evolution of host and pathogen is through characterization of gene flow patterns, which can be measured at many temporal scales. For example, viral gene flow,

manifested as past transmission events, is often inferred by phylogenetic techniques, such as transmission trees and discrete trait analysis with host state reconstruction (Wohl et al. 2016). In comparison, host gene flow is generally assessed using population genetic distance measures, such as F_{ST}, proportion of shared alleles, or relatedness. These measures of gene flow can be subsequently associated with key landscape features to determine resistance to movement and interactions (McRae and Beier 2007) or with environmental factors to identify genetic variation underlying adaptation (Rellstab et al. 2015). These associations presumably form reliable indicators of evolution and transmission between host and pathogen. For example, in white-tailed deer (*Odocoileus virginianus*), landscape features that facilitate gene flow are positively correlated with the transmission of chronic wasting disease, supporting a model of dispersal-mediated disease transmission (Kelly et al. 2014). These kinds of associations, enabled by the increased resolution offered by genomic techniques, will be invaluable for characterizing wildlife diseases in the future.

Coordinating Technology, Data, and Expertise

A practical challenge for landscape genomic applications in wildlife diseases is compiling host, pathogen, and landscape data from disparate databases. In general, efforts to centralize genomic data in publicly available databases, such as GenBank (https://www.ncbi.nlm.nih.gov/genbank), have been successful yet corresponding metadata are often limited. Rather, specialized online databases (e.g., Global Biodiversity Information Facility, http://www.gbif.org/; Herpnet, www.herpnet.org) are repositories for such georeferenced data, but not linked to disease metadata. Furthermore, landscape data, or layers, are scattered across various governmental and organizational websites, such as the National Weather Service (https://www.weather.gov/gis), National Centers for Environmental Information (https://gis.ncdc.noaa.gov/maps/ncei), and the National Land Cover Database (https://www.mrlc.gov/nlcd2011.php). Pathogen data, in addition to their genetic sequences, can also be found in separate microbial (McNeil et al. 2007) and viral (Pickett et al. 2012) databases. Some studies have created species-specific databases, for example, to monitor gene flow and individual identification in pumas using single nucleotide polymorphisms (Fitak et al. 2015), but are not connected to current pathogen datasets such as the Global Mammal Parasite Database (Stephens et al. 2017). A promising approach for better integration could build upon the database constructed by Wardeh et al. (2015), which contains a wealth of information on host–pathogen interactions and their global distribution. Until metadata standards improve and/or a comprehensive database linking together genetic, genomic, and ecological resources for hosts and pathogens to landscape data is developed for wildlife, reliance on collaboration between experts in the fields of pathogen transmission, population genetics, and landscape ecology who are familiar with their respective data resources is crucial.

Understanding the Effects of Rapid Environmental Change

Environments are changing at an unprecedented rate, altering ecosystems through climate change, habitat loss, invasive species introductions, pathogen spillover, and pollution (Acevedo-Whitehouse and Duffus 2009). Among the considerable discussion of global climate change is its potential impact on infectious diseases (Rohr et al. 2011). Perhaps the best example of this phenomenon is the observed correlation between climate change and outbreaks of chytridiomycosis causing worldwide amphibian declines (e.g., Rohr and Raffel 2010). Habitat alteration, fragmentation, and loss are also expected to increase due to expanded urbanization and other human activities on the landscape on a global scale. These anthropogenic changes are known to restrict gene flow in many wildlife host species, changing the dynamics of pathogen invasion and prevalence (Becker et al. 2015; Fountain-Jones et al. 2017), and likely increasing contact between wildlife, domestic animals, and humans; resulting in enhanced rates of cross-species transmission, emerging disease, and zoonotic events (Gale et al. 2009; Miller et al. 2015). Thus, landscape ecology and genomics are critical for tracking the effects of these rapid environmental changes in wildlife disease systems to better mitigate or prevent outbreaks. The discussants advocated approaches such as the examination of recently established natural green spaces in areas of high human activities and recolonized by wildlife species (Baker and Harris 2007) to better understand environmental changes in disease ecology.

Emerging New Questions

The group considered "Emerging new questions" subdivided into 1) in situ models of human diseases, 2) epigenetics and phenotypic plasticity, and 3) evolutionary rates. The discussion noticeably overlapped with aspects of the other 4 themes, particularly on the reexamination of old questions using the strengths of modern genomic data and requiring methodological or statistical advances.

In Situ Models of Human Diseases

In humans, genome-wide association studies (GWAS) are a primary method to identify and characterize loci associated with increased disease risk (Newport and Finan 2011). Most GWAS are largely restricted to noncommunicable, complex diseases while studies of infectious disease risk are less common (Newport and Finan 2011). Furthermore, the general limitations of GWAS, such as small effect sizes, population structuring, statistical power, phenotyping, multiple hypothesis testing, and missing heritability, are not only a concern, but can be exacerbated when investigating infectious diseases. For example, GWAS of infectious diseases are impeded by improper characterization of cases and controls, confounded by infections from subtly different pathogenic strains, and/or inhibited by human polymorphisms conferring variable, or even opposite effects in the presence of different infectious strains (reviewed in Kodaman et al. 2014). In light of these limitations, GWAS of wildlife populations and their associated pathogens may provide an excellent opportunity to understand infectious disease etiology and host resistance to advance comparative biomedicine. Wildlife species serve as reservoirs for 72% of emerging zoonoses (Jones et al. 2008), and are excellent resources to better understand homologous mechanisms of disease resistance. Furthermore, wildlife infectious diseases provide a natural setting through which host–pathogen evolution can be examined; often unabated by the practice of extensive disease-control interventions employed in human and domestic animal medicine (Hart 2011). As such, selection coefficients during disease outbreaks in a wildlife population may be much higher than in humans, generating larger effect sizes and facilitating easier detection using GWAS.

An example of an infectious disease with a wildlife model is plague (*Yersinia pestis*) in prairie dogs (*Cynomys* spp.). Originally, prairie dogs exhibited extreme susceptibility to plague, but recent studies have shown that populations have evolved resistance in Colorado and Texas where plague has been introduced (Rocke et al. 2012). Although the mechanisms of resistance remain unknown, genomic studies are underway. Factors such as the extreme sociality of prairie dogs, which enables rapid colony collapse post outbreak,

make this system an excellent model for the extensive social contacts made by humans that facilitate disease spread.

Another example addresses the extreme lethality of avian malaria to naive hosts in natural populations of multiple bird species in Hawaii (Lapointe et al. 2012). In this case, resistance to malarial infection has evolved in several bird populations (e.g., Atkinson et al. 2013), although the underlying genetic mechanisms remain unclear. These avian *Plasmodium* species are distributed worldwide and share a phylogenetically close relationship to the human malarial parasite (Lapointe et al. 2012). Comparative transcriptomics of the response to malarial infection in birds with that of humans and mice has also shown an evolutionarily conserved response (Videvall et al. 2015), justifying the need for additional research into resistance mechanisms in birds. The discussants recommended genomic approaches including GWAS, pathogen genome-typing, and transcriptomics to benefit not only the conservation and management of wildlife but to provide additional understanding of the diseases in humans and novel targets for therapy and vaccine development.

Epigenetics and Phenotypic Plasticity

Unlike the traditional paradigm of disease resistance evolution in which selection acts on standing genetic variation, individuals can also establish or improve resistance through mechanisms not necessarily encoded in the DNA sequence. This ability for individuals to alter their phenotype in response to environmental changes, such as infections, is called phenotypic plasticity. For example, animals often exhibit various behaviors, such as grooming and self-isolation, that limit both the burden of a parasite or pathogen (resistance) and the associated disease/harm inflicted by that burden (tolerance) (Raberg et al. 2009; Hart 2011). In addition to behavior, these phenotypic changes can be morphological, chemical, physiological, or developmental (Pigliucci et al. 2006). The molecular nature of phenotypic plasticity, or epigenetics, is of immense interest in current biological research, including as it relates to host and pathogen (Gómez-Díaz et al. 2012).

Epigenetics, defined here as environmentally triggered changes in gene regulation independent of DNA sequence variation, has critical roles in both pathogen plasticity and pathogen-induced plasticity in the host (reviewed in Gómez-Díaz et al. 2012). Both pathogen and pathogen-induced examples of epigenetic modifications exist—affecting all known markers of the epigenetic code (i.e., DNA methylation, histone modification, and RNA-mediated silencing) (Gómez-Díaz et al. 2012). For example, the obligate intracellular bacterial pathogen *Anaplasma phagocytophilum* is known to subvert the host immune defense by up-regulating a histone deacetylase which in turn silences host defense genes (Garcia-Garcia et al. 2009). Furthermore, drugs or therapeutic agents targeting epigenetic mechanisms are already being co-opted from oncological applications for use in human disease treatment (Cole et al. 2016).

At present, epigenetics of wildlife diseases remains relatively unexplored. The discussants recognized that time and resources are essential to the development of the conceptual framework and methodologies for application in a natural setting. However, many NGS techniques are being modified to promote epigenetic marker discovery, focused on the sequencing of various types of RNA molecules and the identification of methylated regions of DNA (see methods reviewed by Meaburn and Schulz 2012). The discussants suggested that wildlife disease biologists become increasingly familiar with NGS techniques and conduct epigenetic research of novel disease biomarkers, mechanisms of resistance and tolerance, and therapeutic targets. The future integration of both genomic and epigenetic techniques is important given that diseases exist in many different states along the host–pathogen co-evolutionary trajectory and affords an excellent opportunity for investigating the assimilation of epigenetically controlled plastic phenotypes into genetic variation in wildlife.

Evolutionary Rates

The discussants considered the powerful applications of genomic techniques to investigate the complex array of evolutionary rates among pathogen genomes. Viruses are notorious for evolutionary and mutation rates spanning 5–6 orders of magnitude; making alignment and phylogenetic inference at times a bioinformatic challenge (Duffy et al. 2008). A concerted effort is needed to develop or improve the bioinformatic tools available for inferring the evolutionary history of pathogens, especially at deep time points where mutation saturation or homoplasy masks signals of divergence (Marz et al. 2014). Bioinformatic tools, however, will likely provide only modest improvement on these inferences, and other techniques need to be applied. The best approach could be to continue searching the growing number of available genome sequences of animals for endogenous viral elements (EVEs). These EVEs are parts of viral genomes that have been inserted into the genome of their hosts, often surviving as neutrally evolving pseudogenes. Commonly referred to as viral "fossils," EVEs provide critical sequences for calibrating or informing viral phylogenies (Aiewsakun and Katzourakis 2015). One of the best examples is the discovery of lentiviral EVEs in various mammalian genomes, pushing back the evolutionary origins of lentiviruses at least 60 million years (Hron et al. 2016).

Advances in methods to sequence DNA from ancient, degraded, or otherwise low-quality specimens could be invaluable to informing pathogen origins and evolutionary rates. Viral sequences have already been extracted from ~700 year-old human (Appelt et al. 2014) and caribou (*Rangifer tarandus caribou*; Ng et al. 2014) fecal samples, 1500-year-old Andean mummy bones (Sonoda et al. 2000), and >30 000-year-old permafrost collections (Legendre et al. 2014). Although these studies examined tissues from ideal environments to preserve DNA, the improvement in sensitivity of various sequencing technologies and library preparation methods are expanding the breadth of potential tissue and environment sources (Hofreiter et al. 2015, also see *Methodological and Analytical Advancements* section). In turn, the advances in paleogenomics could provide unprecedented insight into the origin and evolution of pathogens, notably viruses, by assisting in the calibration of rates, recombinations, divergences, and diversifications.

Conclusions

The GDW2017 workshop brought together a culturally and professionally diverse group of researchers and practitioners to train in genomic concepts and techniques. As a result, it was an excellent opportunity to conduct the first horizon scan-like exercise to both assess the current state of genomics and identify the most pressing challenges as they specifically relate to wildlife diseases. Time limitations for the exercise restricted the ability to perform additional rounds of survey and discussion, potentially biasing the discussions in favor of certain topics, such as those posited by the most vocal participants, rather than reaching a true consensus. Although many of the most relevant and promising genomic advances were discussed, as was the intent of the workshop, the specific disadvantages of genomics may have been overlooked. For example, genomic

methodologies are often more expensive, complex, and difficult to validate, which can be problematic for generating rapid, actionable responses to disease outbreaks. Furthermore, these results only offer a brief snapshot of the state of the field and one which is likely to change in light of the rapid genomic advances that have recently occurred and are expected in the future. These advances advocate for periodic horizon scanning or similar activities to monitor progress and prepare for future shifts in the field. Nevertheless, keeping the diverse array of investigators apace with the field of genomics is critical for the successful implementation of programs designed to understand and mitigate the negative impacts of wildlife diseases.

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